CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-704

Administrative/Correspondence Reviews

Paragraph II Certification

Pursuant to 21 U.S.C. Sec. 355(b)(2)(A)(ii) and 21 CFR Sec. 314.50(i)(1)(i)(A)(2), Aventis Pharmaceuticals, Inc. certifies that in the opinion of the company and to the best of its knowledge, patent number 4576604 has expired.

Charlotte L. Barney

Authorized signature of attorney, Agent, Representative or Authorized Official

Date - February 16, 2004

Charlotte L. Barney
Director, Global Patent Litigation

Aventis Pharmaceuticals, Inc.
1041 Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800

Telephone Number
908-231-4551

13. PATENT INFORMATION

Appears This Way
On Original

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 5.

NDA NUMBER: 21-704

NAME OF APPLICANT / NDA HOLDER: Aventis Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Allegra-D 24 Hour

ACTIVE INGREDIENT(S)	STRENGTH(S)
Fexofenadine hydrochloride/Pseudoephedrine Hydrochloride	180mg/240mg

DOSAGE FORM: Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an addional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,578,610	11/26/1996	11/26/2013

d. Name of Patent Owner	Address (of Patent Owner)	
AMR Technology	5429 Main Street P.O. Box 2587	
	City/State: Manchester Center, Vermont	
	ZIP Code: 05255-2587	FAX Number (if available): 802-362-3264
	Telephone Number: 802-362-5158	E-Mail Address (if available): dwidw@albanmolecular.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* Claim 11 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or intended use information as identified specifically in the approved labeling.)*

Patent Claims generally: A method of treating allergic reactions in a patient.

The proposed INDICATIONS AND USAGE are as follows:

ALLEGRA-D 24 HOUR Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/and/or throat, itchy/watery/red eyes, and nasal congestion.

ALLEGRA-D 24 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired (see CLINICAL PHARMACOLOGY).

5. No Relevant Patents

DEC. 11. 2003 12:02PM PATENT LITIGATION NO. 5820 P. 5

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

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FORM FDA 3542a (7/03) Page 3

Best Possible Copy

DEC. 11. 2003 12:02PM PATENT LITIGATION NO. 5820 P. 6

8. Declaration Certification

8.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I assert that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

***Warning:** A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.*

8.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

Charlotte L. Barney

Date Signed: 12/4/03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(e)(4) and (f)(4).

Check applicable box *and provide information below.*

☒ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Charlotte L. Barney
Director, Global Patent Litigation

Address	City/State
Aventis Pharmaceuticals Inc. 1041 Route 202-206 P.O. Box 6800	Bridgewater, New Jersey
Zip Code 08807-0800	**Telephone Number** 908-231-4551
FAX Number *(if available)* 908-231-2840	**E-Mail Address** *(if available)* charlotte.barney@aventis.com

Notes to Form FDA 3542a for U.S. Patent 5,578,610 for NDA 21-704 (Allegra-D 24 Hour):

Note to Question 2.2. U.S. Patent 5,578,610 claims one of the active ingredients of the drug product Allegra-D 24 Hour (fexofenadine) as a substantially pure compound, and these claims are not limited to specific polymorphic forms. However, the patent does not specifically claim any particular polymorph of the active ingredient fexofenadine, and therefore the answer to Question 2.2 is "no".

Department of Health and Human Services
Food and Drug Administration

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NDA NUMBER
21-704

NAME OF APPLICANT / NDA HOLDER
Aventis Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Allegra-D 24 Hour

ACTIVE INGREDIENT(S)	STRENGTH(S)
Fexofenadine hydrochloride/Pseudoephedrine hydrochloride	180mg/240mg

DOSAGE FORM
Tablet

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Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,004,582	12/21/1999	5/29/2018

d. Name of Patent Owner	Address (of Patent Owner)	
Ganotica Corp.	c/o Alfaro, Tarrer, Ramirez P.O. Box 915 R.G. Hodge Plaza, 2nd Floor Upper Main Street	
	City/State Road Town, Tortola British Virgin Islands	
	ZIP Code	FAX Number (if available) 54 11 4379-4116
	Telephone Number 54 11 4379-4213	E-Mail Address (if available) jfacur@rosentics.com.ar

a. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 7.a.)	
○ Rick Matos, Ph.D. Innovar, L.L.C. Innovative Patents and Technologies	8108 Fleetwood Drive P.O. Box 250647	
	City/State Plano, TX	
	ZIP Code 75025-0647	FAX Number (if available) 972-747-7575
	Telephone Number 972-747-7373	E-Mail Address (if available) innovarllc@sbcglobal.net

7. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

9. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of the declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For the pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

5. Declaration Certification

5.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

5.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Charlotte L. Barney

Date Signed: 12/4/03

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Check applicable box and provide information below.

☒ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Charlotte L. Barney
Director, Global Patent Litigation

Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 P.O. Box 6800	City/State Bridgewater, NJ
ZIP Code 08807-0800	Telephone Number 908-231-4551
FAX Number (if available) 908-231-2840	E-Mail Address (if available) charlotte.barney@aventis.com

The public reporting burden for this collection of information has been estimated to average 4 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 3542a (7/03) Page 4

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
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See OMB Statement on Page 3

NDA NUMBER: 21-704

NAME OF APPLICANT / NDA HOLDER: Aventis Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Allegra-D 24 Hour

ACTIVE INGREDIENT(S): Fexofenadine hydrochloride/Pseudoephedrine hydrochloride

STRENGTH(S): 180mg/240mg

DOSAGE FORM: Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number: 6,037,353

b. Issue Date of Patent: 3/14/2000

c. Expiration Date of Patent: 3/17/2017

d. Name of Patent Owner: Merrell Pharmaceuticals, Inc.

Address (of Patent Owner): 3711 Kennett Pike, Suite 200

City/State: Greenville, DE

ZIP Code: 19807

FAX Number (if available): 302-777-7665

Telephone Number: 302-777-7222

E-Mail Address (if available):

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03)

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement:		
2. Drug Substance (Active Ingredient)		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No
3. Drug Product (Composition/Formulation)		
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No
4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* Claims 1, 2, 3, 4, 5 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.3a If the answer to 4.2 is ____ Use: *(Submit indication or method of use information as described specifically in the approved labeling.)*		

"Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Patent Claims generally: A method of treating a histamine-mediated condition in a patient having impaired liver function due to disease or due to administration of a concomitant drug which inhibits normal liver metabolic function while avoiding cardiac events associated with administration of terfenadine.

The proposed INDICATIONS AND USAGE, a relevant section from proposed PRECAUTIONS (Drug Interactions), and a relevant section from proposed CLINICAL PHARMACOLOGY (Special Populations—Hepatically Impaired) are as follows:

INDICATIONS AND USAGE

ALLEGRA-D 24 Hour Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itch nose/palate and/or throat, itchy/watery/red eyes, and nasal congestion.

ALLEGRA-D 24 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired (see CLINICAL PHARMACOLOGY).

PRECAUTIONS

Drug Interactions

Fexofenadine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly.

Co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine hydrochloride 120 mg twice daily was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions in normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole.

The mechanism of these interactions has been evaluated in in vitro, in situ and in vivo animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In vivo animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Due to the pseudoephedrine component, ALLEGRA-D 24 HOUR is contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (eg, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of ALLEGRA-D 24 HOUR concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

CLINICAL PHARMACOLOGY

Special Populations

Pharmacokinetics in special populations (ie, renal, hepatic impairment, and age), obtained after a single dose of 60 mg fexofenadine hydrochloride, were compared to those from normal volunteers in a separate study of similar design.

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in subjects with hepatic disease did not differ substantially from that observed in healthy volunteers. The effect on pseudoephedrine pharmacokinetics is unknown.

5. No Relevant Patents

For the pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

8. Declaration Certification

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☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
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Director, Global Patent Litigation

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ZIP Code 08807-0800	Telephone Number 908-231-4551
FAX Number (if available) 908-231-2840	E-mail Address (if available) charlotte.barney@aventis.com

Department of Health and Human Services
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Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 2.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 21-704

NAME OF APPLICANT / NDA HOLDER: Aventis Pharmaceuticals Inc

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Allegra-D 24 Hour

ACTIVE INGREDIENT(S)	STRENGTH(S)
Fexofenadine hydrochloride/Pseudoephedrine hydrochloride	180mg/240mg

DOSAGE FORM: Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewritten versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,187,791	2/13/2001	5/11/2012

d. Name of Patent Owner: Cardeam Capital L.P.

Address (of Patent Owner): c/o Westbroke Ltd.
Richmond House Par-La-Ville Road
P.O. Box HM 1022
City/State: HMR DX Hamilton, Bermuda
ZIP Code:
FAX Number (if available): 441-292-0865
Telephone Number: 441-292-3334
E-Mail Address (if available):

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Louis J. Willc
Vice President, Global Patent Litigation

Address (of agent or representative named in 1.e.): Aventis Pharmaceuticals Inc.
1041 Route 202-206
P.O. Box 6800
City/State: Bridgewater, New Jersey
ZIP Code: 08807-0800
FAX Number (if available): 908-231-2691
Telephone Number: 908-231-5721
E-Mail Address (if available): louis.wille@aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

FORM FDA 3542a (7/03)

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

Appears This Way
On Original

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number (as listed in the patent) Claims 1, 2, 3, 6, 7, 8, 9 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.3a	If the answer to 4.2 is ____ Use. *(Submit indication or method of use information as labeled specifically in the approved labeling.)*		

"Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Patent Claims generally: A method of treating a histaminic or histamine-related condition or disease, or providing an antihistaminic effect to 1) patients susceptible to possible cardiac events associated with the administration of terfenadine; 2) humans while avoiding the concomitant liability of cardiac arrythmias associated with the administration of terfenadine; or 3) patients susceptible to QT prolongation and/or ventricular tachycardia when using terfenadine. The proposed INDICATIONS AND USAGE, a relevant section from proposed PRECAUTIONS (Drug Interactions), and a relevant section from proposed CLINICAL PHARMACOLOGY (Special Populations—Hepatically Impaired) are as follows: INDICATIONS AND USAGE ALLEGRA D 24 Hour Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itch nose/palate and/or throat, itchy/watery/red eyes, and nasal congestion. ALLEGRA-D 24 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired (see CLINICAL PHARMACOLOGY) PRECAUTIONS Drug Interactions Fexofenadine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly. Co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine hydrochloride 120 mg twice daily was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole. The mechanism of these interactions has been evaluated in vitro, in rats and in vivo animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In vivo animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion. Due to the pseudoephedrine component, ALLEGRA-D 24 HOUR is contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (eg, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of ALLEGRA-D 24 HOUR concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS). CLINICAL PHARMACOLOGY Special Populations Pharmacokinetics in special populations (for renal, hepatic impairment, and age), obtained after a single dose of 60 mg fexofenadine hydrochloride, were compared to those from normal volunteers in a separate study of similar design. Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in subjects with hepatic disease did not differ substantially from that observed in healthy volunteers. The effect on pseudoephedrine pharmacokinetics is unknown.
6. No Relevant Patents	

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

Appears This Way
On Original

8. Declaration Certification

8.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I swear that I am familiar with 21 CFR 314.53 and that submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

8.2 Authorized Signature of NDA applicant/holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Charlotte L. Barney

Date Signed: 12/4/03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Charlotte L. Barney
Director, Global Patent Litigation

Address	City/State
Aventis Pharmaceuticals Inc. 1041 Route 202-206 P.O. Box 6800	Bridgewater, New Jersey
Zip Code 08807-0800	**Telephone Number** 908-231-4551
FAX Number *(if available)* 908-231-2840	**E-mail Address** *(if available)* charlotte.barney@aventis.com

FORM FDA 3542a (7/03)

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 21-704

NAME OF APPLICANT / NDA HOLDER: Aventis Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Allegra-D 24 Hour

ACTIVE INGREDIENT(S): Fexofenadine hydrochloride/Pseudoephedrine hydrochloride

STRENGTH(S): 180mg/240mg

DOSAGE FORM: Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,399,632	6/4/2002	7/11/2011

d. Name of Patent Owner	Address (of Patent Owner)	
Cardarm Capital L.P.	c/o Wembrake Ltd. Richmond House Par-La-Ville Road P.O. Box HM 1022	
	City/State HMR DX Hamilton, Bermuda	
	ZIP Code	FAX Number (if available) 441-292-0865
	Telephone Number 441-292-3434	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
☞ Louis J. Wille Vice President, Global Patent Litigation	Aventis Pharmaceuticals Inc. 1041 Route 202-206 P.O. Box 6800	
	City/State Bridgewater, New Jersey	
	ZIP Code 08807-0800	FAX Number (if available) 908-231-3691
	Telephone Number 908-231-5721	E-Mail Address (if available) lou_wille@aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

Appears This Way
On Original

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.		
2. Drug Substance (Active Ingredient)		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No
3. Drug Product (Composition/Formulation)		
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No
4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is Use: *(Submit indication or method of use information as it is listed specifically in the approved labeling.)*		

"Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Patent Claims generally: A method of treating a histamine-mediated condition or providing/obtaining an antihistaminic effect in a 1) a patient in whom terfenadine is not metabolized at the normal rate to the terfenadine acid metabolite, while avoiding the concomitant liability of cardiac arrythmias associated with the administration of terfenadine; 2) a patient in whom terfenadine is not metabolized at the normal rate to the terfenadine acid metabolite; 3) a patient in whom terfenadine is not metabolized at the normal rate to terfenadine acid metabolite and who is subject to QT prolongation and/or ventricular tachycardia when using terfenadine; or 4) a human who also received a product which inhibits terfenadine metabolism.

The proposed INDICATIONS AND USAGE, a relevant section from proposed PRECAUTIONS (Drug Interactions), and a relevant section from proposed CLINICAL PHARMACOLOGY (Special Populations—Hepatically Impaired) are as follows:

INDICATIONS AND USAGE

ALLEGRA-D 24 Hour Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itch nose/palate and/or throat, itchy/watery/red eyes, and nasal congestion.

ALLEGRA-D 24 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired (see CLINICAL PHARMACOLOGY).

PRECAUTIONS

Drug Interactions

Fexofenadine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly.

Co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine hydrochloride 120 mg twice daily was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole.

The mechanism of these interactions has been evaluated in in vitro, in situ and in vivo animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In vivo animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Due to the pseudoephedrine component, ALLEGRA-D 24 HOUR is contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (eg, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of ALLEGRA-D 24 HOUR concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

CLINICAL PHARMACOLOGY

Special Populations

Pharmacokinetics in special populations (for renal, hepatic impairment, and age), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those from normal volunteers in a separate study of similar design.

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in subjects with hepatic disease did not differ substantially from that observed in healthy volunteers. The effect on pseudoephedrine pharmacokinetics is unknown.

6. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

8. Declaration Certification

8.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

8.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

Charlotte L. Barney

Date Signed: 12/4/03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(d)(4) and (f)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Charlotte L. Barney
Director, Global Patent Litigation

Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 P.O. Box 6800	City/State Bridgewater, New Jersey
Zip Code 08807-0800	Telephone Number 908-231-4551
FAX Number *(if available)* 908-231-2840	E-Mail Address *(if available)* charlotte.barney@aventis.com

FORM FDA 3542a (7/03)

Amended Certification Pursuant to 21 Sec. C.F.R. 314.50(i)(6)

Paragraph IV Certification

Pursuant to 21 U.S.C. Sec. 355(b)(2)(A)(iv), 21 CFR Sec. 314.50(i)(1)(i)(A)(4), and 21 CFR Sec. 314.50(i)(3), Aventis Pharmaceuticals, Inc. certifies that Patent Number 4801461 will not be infringed by the manufacture, use or sale of Allegra-D® 24 Hour (fexofenadine HCl 180mg/pseudoephedrine HCl 240 mg) Extended Release Tablets, for which this application is submitted. The patent owner, ALZA Corporation, has granted Aventis Pharmaceuticals, Inc. a patent license.

Charlotte L Barney

Authorized signature of attorney, agent, representative or authorized official

Date - October 12, 2004

Charlotte L. Barney
Director, Global Patent Litigation

Aventis Pharmaceuticals, Inc.
1041 Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800

Telephone Number
908-231-4551

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

October 12, 2004

Badrul Chowdhury, M.D., Ph.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products (HFD-570)
Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705

NDA 21-704
ALLEGRA-D 24 HOUR™ Extended Release Tablets
AMENDMENT TO PENDING APPLICATION
Amendment 07: Patent Certification

Dear Dr. Chowdhury:

Reference is made to NDA 21-704 ALLEGRA-D 24 HOUR™ Extended-Release Tablets (fexofenadine hydrochloride 180mg and pseudoephedrine hydrochloride 240mg) submitted to the Agency on December 19, 2003 and currently under review with a PDUFA action goal date of October 19, 2004.

The enclosed Amendment 07 to this pending application contains information for Item 14, Patent Certification. Pursuant to 21 CFR §314.50(i)(6), Aventis Pharmaceuticals, Inc. ("Aventis") hereby notifies the Agency that the above referenced application is amended to change the certification previously provided under Section 505(b)(2)(A) from Paragraph III to Paragraph IV. ALZA Corporation ("Alza"), the owner of Patent No. 4801461, has granted Aventis a license for ALLEGRA-D 24 HOUR™ Extended-Release Tablets (fexofenadine hydrochloride 180mg and pseudoephedrine hydrochloride 240mg). Included with this amendment (Patent Information, Item 13) is Alza's consent to an immediate effective date upon approval of this NDA.

NDA 21-704 was submitted with an electronic archival copy (e-NDA) in accordance with current guidance for electronic submissions according to Form 356h NDA format. In compliance with that guidance, the enclosed Amendment is also submitted with an electronic archival copy.

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

Aventis considers the information included in this submission to be confidential and proprietary, and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis according to CFR §314.430.

On behalf of Aventis, we look forward to continuing to work with the Division to facilitate the review of this application. If you have any questions or need additional information during the review, please contact the undersigned, Kimberly S. Stranick, Ph.D., at (908) 304 6580 or, in my absence, Eric A. Floyd, Ph.D., at (908) 231 2474.

Sincerely,

Kimberly S. Stranick

Kimberly S. Stranick, Ph.D.
Director, Regulatory Liaison
US Regulatory Affairs

Attachment
Enclosures:
Electronic archival copy: 1 CD-ROM labeled *NDA 21-704 ALLEGRA-D 24 HOUR™ Extended Release Tablets, Amendment to Pending Application, Amendment 07 October 12, 2004, CMC*
1 paper copy of Cover Letter, Form FDA356h and Item 14 with original signatures

cc: Ms. Christine Yu, Regulatory Project Manager

NDA 21-704 Electronic Submission Information

Description Format (Electronic/Paper)

Item	Description	Electronic	Paper
	Cover Memo	X	X
	Form 356h	X	X
1	Index	X	
2	Labeling		
3	Application Summary		
4	Chemistry		
5	Nonclinical Pharmacology & Toxicology		
6	Human Pharmacokinetics and Bioavailability		
7	Clinical Microbiology		
8	Clinical		
9	Safety update report		
10	Statistical		
11	Case Report Tabulations		
12	Case Report Forms		
13	Patent Information	X	
14	Patent Certification	X	X
15	Establishment Description		
16	Debarment Certification		
17	Field Copy Certification		
18	User Fee Cover Sheet		
19	Financial Information		
20	Other		

Electronic Submission Summary

Media Type and Number: 1 CD-ROM
File Formats: Portable Document Format (.pdf)
Total Size: Electronic Submission – approximately 1 MB

Virus Verification:

Aventis certifies that all electronic media are free from computer virus. The virus scan was performed using Symantec's Norton Antivirus Corporate Edition, Program Version 7.50.846, Scan Engine Version 4.1.0.6. The Virus Definition File is Version 61006t, issued October 6, 2004.

Sponsor Contact:

Regulatory Affairs

Kimberly S. Stranick, Ph.D.
Director, Regulatory Liaison
US Regulatory Affairs
Aventis Pharmaceuticals, Inc.
908 304 6580
908 812 9270 mobile
908 304 6317 fax

EXCLUSIVITY SUMMARY FOR NDA # 21-704 SUPPL #_____

Trade Name Allegra-D 24 Hour ER Tablet
Generic Name (fexofenadine HCl 180 mg/pseudoephedrine HCl 240mg)

Applicant Name Aventis Pharmaceuticals HFD # HFD-570

Approval Date If Known 10/19/04

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_✓__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /_✓__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Aventis conducted two PK studies to support this NDA, but they also monitored safety endpoints, such as AE's, vital signs, physical exams, clinical labs, ECG's.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_✓__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_✓__/ NO /___/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✓__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_✓__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-021 Efidac 24(pseudoephedrine HCl) ER tablet

NDA# 20-625 Allegra (fexofenadine HCl) capsule

NDA# 20-872 Allegra 30, 60, 180 mg (fexofenadine HCl) tablets

NDA# 20-786 Allegra-D ER (fexofenadine 60mg/PSE 120mg) tablet

Others...

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) *If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a).* If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_✓__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this

section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /_✓__/ NO /___/

Investigation #2 YES /_✓__/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study M106455B/3081 NDA 20-872

Study PJPR0027 NDA 20-872

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_✓__/

Investigation #2 YES /___/ NO /_✓__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) ***If the answers to 3(a) and 3(b) are no,*** identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ Date_____

Christine Yu, R.Ph.
Regulatory Project Manager

_____ Date_____

Badrul A. Chowdhury
Director, Division of Pulmonary & Allergy Drug Products

Form OGD-011347 Revised 05/10/2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
10/20/04 02:29:00 PM

Aventis

Debarment Certification

December 1, 2003

Aventis Pharmaceuticals, Inc. hereby certifies that it has not used and will not use in any capacity the services of any person debarred pursuant to section 306(a) and (b) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

Eric A. Floyd for S.C.

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs
Tel (908) 231 5863 or (908) 304 6580

19. FINANCIAL INFORMATION FOR INVESTIGATORS

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Dennis N. Morrison, D.O. Investigator, S/1001, S/1002	[ ]
	[ ]	
	[ ]	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Steve Caffe, M.D.	Vice President, Head US Regulatory Affairs
FIRM/ORGANIZATION	
Aventis Pharmaceuticals, Inc.	
SIGNATURE	**DATE**
Erin d. Hyg for S.C.	12/01/2003

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (2/03)

Created by: PSC Media Arts (301) 443-1090 EF

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Original NDA 21-704	Efficacy Supplement Type SE-	Supplement Number	
Drug: Allegra-D 24 Hour ER tablet (Fexofenadine HCl 180mg/PSE HCl 240mg)		Applicant: Aventis Pharmaceuticals, Inc	
RPM: Christine Yu, R.Ph.		HFD-570	Phone # 301-827-1051

Application Type: ( ) 505(b)(1) (✓) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (✓) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
User Fee Goal Dates	October 19, 2004
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee ***Supplement fee agreed upon by Agency***	( ) Paid UF ID number 4443
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No

• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(✓) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (✓) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) (✓) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No (✓) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (✓) No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	9/10/04

Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only) ***will do after approval***	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	10/18/04
• Most recent applicant-proposed labeling	10/13/04
• Original applicant-proposed labeling	12/19/03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS- 7/1/2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	9/29/04
• Reviews	DMETS- 7/1/2004 See each discipline review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	1/29/02 under IND 48,486
• Pre-NDA meeting (indicate date)	8/27/03 under IND 66,289
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	10/19/04 Director 10/13/04- Medical Team Leader
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/5/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	10/5/04 (in MOR)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	5/26/04
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9/24/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	9/2/04
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	10/18/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	10/18/04
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: (✓) Acceptable 10/4/04 ( ) Withhold recommendation
❖ Methods validation ***Will not be requested see CMC review page 98***	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/30/04
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

8 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DIVISION DIRECTOR'S MEMORANDUM

Date: October 19, 2004

To: NDA 21-704

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Allegra-D 24 Hour (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) Extended-Release Tablets

Applicant: Aventis Pharmaceuticals, Inc.

Administrative and Introduction

Aventis Pharmaceuticals submitted NDA 21-704 for Allegra-D 24 Hour (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) Extended-Release Tablets on December 19, 2003. The PDUFA due date on this application is October 19, 2004. Allegra-D 24 Hour Tablets is proposed for prescription use in patients 12 years of age and older for relief from symptoms of seasonal allergic rhinitis. The product is particularly intended to be used when both the antihistaminic properties of fexofenadine and the nasal decongestant properties of pseudoephedrine are desired. The proposed dose is one tablet once a day. Aventis has three products containing fexofenadine approved for marketing in United States. These are Allegra Capsules (fexofenadine HCl 60 mg, NDA 20-625), Allegra Tablets (fexofenadine HCl 30 mg, 60 mg, and 180 mg, NDA 20-872), and Allegra D Tablets (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg, NDA 20-786). The currently marketed Allegra D product is dosed twice daily. Since fexofenadine and pseudoephedrine are both approved marketed products, no clinical efficacy or safety studies were required. The clinical program for this application consists of bioequivalence studies with supported safety data. Aventis also included summaries of two clinical studies that were previously submitted to NDA 20-872 to further support this application. The submitted clinical data support approval of this application. Although there are no outstanding issues from any disciplines that would preclude approval of this application, Aventis informed the Division on September 22, 2004, of significant manufacturing process changes that would require approval of a prior approval CMC supplement before Aventis can market products manufactured with the new process.

Aventis Pharmaceuticals originally submitted this NDA as a 505(b)(1) application. However, because Aventis does not have ownership of the data for extended-release pseudoephedrine, this NDA should have been submitted as a 505(b)(2) application. The Division notified Aventis, and Aventis amended the NDA on February 17, 2004, to a 505(b)(2) application with initial Paragraph 2 and 3 certifications, followed by Paragraph 4 certification on October 12, 2004. Aventis has entered into a licensing agreement with the owner of the extended-release pseudoephedrine data (ALZA Corporation) and has

submitted appropriate patent certification to the Agency. Aventis has submitted a letter to the NDA from ALZA which states "ALZA does not intend to file an action for patent infringement against Aventis or its affiliates or sublicensees" based on a claim of patent infringement. "Further, ALZA consents to FDA's approval of Aventis' 505(b)(2) application for Allegra-D 24 Hour with an immediate effective date on or after the date of this letter." Virginia Beakes of the Office of Regulatory Policy has checked with the Office of Chief Council and has informed the Division that this NDA may be approved from a regulatory standpoint.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation
Allegra-D 24 Hour contains active drug substances pseudoephedrine in a sustained release [ ] and fexofenadine HCl in an immediate release outer coat, and a number of commonly used excipients. The [ ] which contains [ ] is [ ] the control release of pseudoephedrine via a well known [ ] mechanism. Fexofenadine HCl drug substance is produced by Aventis and pseudoephedrine HCl drug substance is produced by [ ] The pseudoephedrine [ ] are manufactured at a site in [ ] all subsequent manufacturing and packaging are performed at Aventis site in Kansas City. All manufacturing sites related to this application have acceptable evaluation status.

On September 22, 2004, Aventis informed the Division that they have installed new equipment [ ] that has affected the dissolution profiles of the tablets. This is a substantial change and would require data to link the tablets manufactured with the new equipment to the tablets manufactured with the old equipment that was originally submitted for Agency review. Other than this major issue, there were some minor CMC issues that were resolved during review of the application. There are also some minor deficiencies that will not impact the safety or efficacy of the drug product, which the applicant has agreed to resolve post-approval. These are discussed in detail in Dr. Jao's excellent review. The CMC team has recommended an approval action on this application, and I concur with that recommendation. This recommendation is for the drug product produced with the original equipment that was submitted to the Agency and was fully reviewed. Aventis will need to submit a pre-approval supplement before they can market products manufactured with the new equipment.

Clinical Pharmacology and Biopharmaceutics, and Clinical
The applicant submitted results of three clinical pharmacology studies and a summary of safety data. Of the three clinical pharmacology studies two were conducted with the to-be-marketed formulation and were considered relevant to this NDA. The two clinical pharmacology studies were conducted in healthy male and female volunteers between the ages of 18 and 44 years. The studies were designed to show bioequivalence of Allegra-D 24 Hour to the reference products after a single dose and at steady state (Study M106455S/1001), and to assess the effect of high fat high calorie diet on the absorption of fexofenadine and pseudoephedrine from Allegra-D 24 Hour Tablets (Study

M106455S/1002). Reference products used were marketed fexofenadine HCl 180 immediate-release Tablets (Allegra) and pseudoephedrine HCl 240 mg extended-release (Sudafed 24 Hour) Tablets. The clinical pharmacology studies were reviewed in depth by the Office of Clinical Pharmacology and Biopharmaceutics (OCBP) Reviewer Dr. Al-Habet, and all submitted studies and additional safety data were reviewed by Medical Officer Dr. Lee. The OCBP team concluded that the pharmacokinetic profiles of Allegra-D 24 Hour are sufficiently similar to those of the reference listed drugs to support approval, and I concur with that conclusion.

The Cmax and AUC data from the two studies are shown in Table 1. For the single dose and multiple dose bioequivalence study the 90% CI were within the accepted 80% to 125% bioequivalence limit. The food effect study showed that food produced a large effect on fexofenadine, but not on pseudoephedrine (Table 1).

Table 1. Ratio between test and reference products (test/reference) for geometric LS mean values of PK parameters of fexofenadine and pseudoephedrine from various studies

		Fexofenadine		Pseudoephedrine	
	PK parameter	Point estimate	90% CI	Point estimate	90% CI
Study 1001 (Single dose) *					
	Cmax	101.4	89.6-114.8	106.4	102.1-110.9
	AUC inf	102.4	94.5-111.1	93.6	89.8-97.5
Study 1001 (Steady state) *					
	Cmax	108.0	96.7-120.7	103.4	97.9-109.1
	AUC inf	102.8	94.5-112.0	95.1	90.2-100.2
Study 1002 (Food effect) †					
	Cmax	45.8	37.9-55.4	91.2	86.2-96.6
	AUC inf	58.4	51.0-66.9	90.7	87.8-93.8

* Reference drugs: Marketed fexofenadine HCl 180 immediate-release Tablets (Allegra) and pseudoephedrine HCl 240 mg extended-release (Sudafed 24 Hour) Tablets
† Single Allegra-D 24 Hour Tablet administered 30 minute after high-fat breakfast

Literature report suggests that bioavailability of fexofenadine is affected by fruit juices such as grapefruit juice and apple juice. At the end-of-phase 2 meeting the Division asked Aventis to investigate the effect of fruit juices on fexofenadine. At the Division's request Aventis submitted results of these investigations during the review cycle. The submission included three studies (Studies 4141, 4143, and 4144) that assessed histamine induced skin wheal and flare response coupled with population pharmacokinetic analysis. These studies are reviewed in detail by the OCBP reviewer Dr. Al-Habet. These studies showed that grapefruit juice or orange juice reduced the exposure of fexofenadine by approximately 36%. The size of histamine induced skin wheal and flare was larger when fexofenadine was administered with either grapefruit juice or orange juice compared to water. The effect of food and fruit juices on the exposure of fexofenadine is substantial and is likely to affect the clinical efficacy of fexofenadine. The product label will reflect the findings of these studies and the label will state that the drug should be taken on empty stomach with water.

Review of the safety data in the clinical pharmacology studies and two clinical studies that were submitted to NDA 20-872 did not reveal any safety signal. Review of the literature and US AERS database do not raise any safety concerns.

The clinical pharmacology studies were conducted in subjects down to the age of 18 years, but the applicant is seeking approval down to the age of 12 years. This is acceptable because the pharmacokinetic parameter is not expected to be different between children 12 through 18 years of age and subjects over 18 years of age. The safety is also not expected to be different in the 12 to 18 years age group.

Pharmacology and Toxicology
The applicant did not conduct any new preclinical studies for this application because the active components of Allegra-D 24 Hour were previously studied by Aventis or others.

Data Quality, Integrity, and Financial Disclosure
There was one study center and one analytical site for the two clinical pharmacology studies. DSI audited the study center. No serious deficiencies were noted, DSI recommended acceptance of the studies. During review of these studies no issues with data quality and integrity were noted. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues were present.

Pediatric Considerations
The applicant is proposing an indication down to the age of 12 years and is not proposing to seek approval in patients below 12 years of age. This is acceptable because the fixed dose combination at the proposed dosage would not be suitable for children younger than 12 years of age.

Product Name
The trade name Allegra is approved and used by Aventis for the product line containing fexofenadine. The suffix "D 24 Hour" distinguishes this product as containing a decongestant and that the dosing frequency is 24 hours. DMETS and DDMAC find the proposed trade name acceptable. Aventis has submitted a supplemental application to the Agency to change the currently marketed Allegra D product to Allegra-D 12 Hour to distinguish the two products. This is reasonable. That application is currently under review.

Labeling
Aventis submitted a product label that generally conforms to the currently marketed Allegra and Allegra D product labels. The label has been reviewed by various disciplines. The Division and Aventis have agreed on a final labeling text. During comparative review of all labels containing fexofenadine the Division identified some differences and inconsistencies among the labels. For example, the drug interaction

information and food effect information was not consistent across the labels. The Division has communicated the inconsistencies to Aventis. The label of all products containing fexofenadine will be harmonized to make them consistent.

Action

The clinical pharmacology data and clinical safety data are sufficient to support approval of Allegra-D 24 Hour Tablets for use in patients ages 12 years and older for control of symptoms of seasonal allergic rhinitis. The CMC data also support approval of the product that was manufactured with the method proposed in the original application. Therefore, the action on this application will be APPROVAL. As stated above under the CMC section, Aventis will need to submit a prior approval supplement with supporting data to market the product manufactured with the process modification that Aventis mentioned to the Agency late in the review cycle.

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/s/

Badrul Chowdhury
10/19/04 01:03:11 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 6, 2004

To: Kimberly S. Stranick, Ph.D. Director, US Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6317	**Fax number:** 301-827-1271
Phone number: 908-304-6580	**Phone number:** 301-827-1051

Subject: FDA proposed Package Inserts for NDA 21-704 Allegra-D 24 hour and NDA 20-786/S-017 Allegra-D 12 hour.
Allegra products comparison table for reference

Total no. of pages including cover: 25

Comments: **** Provide response to this correspondence as soon as possible, but no later than 12:00 PM Friday, October 8, 2004. ****

Document to be mailed: ☐ YES √ NO

25 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Yu
10/6/04 04:28:52 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: October 15, 2004

To: Kimberly S. Stranick, Ph.D. Director, US Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6317	**Fax number:** 301-827-1271
Phone number: 908-304-6580	**Phone number:** 301-827-1051

Subject: NDA 21-704 Allegra-D 24 hour CMC agreements

Total no. of pages including cover: 2

Comments: ** **Please respond as soon as possible, no later than 12:00 pm Monday, October 18, 2004.** **

Document to be mailed: ☐ YES √ NO

We acknowledge your CMC amendments to NDA 21-704 dated August 26 and September 29, 2004. Your agreements to 1-4 below are acceptable. We must receive an agreement for the *new* commitment 5 below before this NDA may be approved. We request that you submit a formal response to the NDA agreeing to all five commitments.

1. Agree to revise the drug product specifications according to the proposed agreements contained in your amendments dated August 26, 2004 and September 29, 2004.

   a. Method [ ] will be used for drug product identification.
   b. The acceptance criterion for Total Degradation Products during shelf-life is NMT [ ]
   c. The acceptance criterion for [ ] is NMT [ ] µg/tablet, and for [ ] is NMT — µg/tablet. These acceptance criteria are implemented on an interim basis and subject to reexamination based on data from approximately —batches of post approval commercial production.

2. Agree to revise the system suitability testing [ ] for the following analytical methods according to the proposed agreements contained in your amendment dated September 29, 2004:

   a. NMT [ ] for the system suitability testing [ ] for fexofenadine HCl and pseudoephedrine HCl.
   b. NMT [ ] for the system suitability [ ] method for [ ]
   c. NMT [ ] for the system suitability injections in the HPLC testing method for Dissolution.

3. The following pertains to expiry dating and holding time:

   a. Agree (as per your amendment dated August 26, 2004) that the expiry-dating clock starts [ ] at your Kansas City site.
   b. A 24-month expiry dating is acceptable for the drug product packaged in 30ct, 100ct,[ ] HDPE bottle.
   c. A [ ] holding time is acceptable for bulk drug product packaged in [ ] and [ ] holding time is acceptable for bulk drug product packaged [ ]. As per your amendment dated August 26, 2004, agree to perform an additional hold study to confirm that the finished tablets stored in these bulk containers for the time periods indicated above, and then packaged in bottles (30 ct [ ] and blisters, remain within specification throughout the proposed shelf life of 24 month.
   d. A [ ] holding time is acceptable for [ ] pseudoephedrine — a [ ] holding time is acceptable for [ ] pseudoephedrine — and a — total holding time for [ ] combined is acceptable.

4. Agree to continue [ ] of the HDPE bottles at the [ ] stability time points for the NDA stability batches to further demonstrate the effectiveness of the carbon canister throughout the remaining proposed shelf life of the product, as stated in amendment dated August 26, 2004.

5. Your stability database did not include [ ] blister physician sample. However, based on the supporting stability testing data of [ ] blister, an eighteen (18) month expiry dating is acceptable for the drug product packaged as [ ] blister physician samples; provided you agree to conduct both long term and accelerated stability testing on this presentation for the first three (3) commercial batches, and include this presentation in your regular annual stability testing protocol. For future reference, all to-be-marketed packaging configurations (including physician samples) should be included in your NDA filings and annual stability protocols.

If you have questions about the contents of this facsimile, please contact Ms. Christine Yu at 301-827-1051.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: September 13, 2004

To: Kimberly S. Stranick, Ph.D. Director, US Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6317	**Fax number:** 301-827-1271
Phone number: 908-304-6580	**Phone number:** 301-827-1051

Subject: NDA 21-704 Allegra-D 24h
CMC and container labeling comments

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES √ NO

We refer to your NDA 21-704 and have the following comments and requests for information. Submission of timely responses would be appreciated.

1. The following comments pertain to drug product specifications:

   a. Revise the acceptance criteria for [ ] to be reflective of the data:

	Proposed	Release data	Suggested
[			]
[			]

Taking into account the complexity of the process and limited manufacturing experience, the Agency suggested data-based acceptance (which is twofold higher than any observed value) should be implemented on an interim basis and subjected to reexamination based on sufficient data from post approval commercial productions (e.g., approximately —batches).

2. The following comments pertain to analytical method validations:

   a. Tighten and submit revised [ ]

   b. Tighten and submit revised [ ]

   c. Tighten and submit revised [ ]

3. The following comments pertain to labeling:

   a. For all container labels:

      i. Relocate the "Rx only" statement to the principal display panel.
      ii. Revise the "Dosage and Administration" statement to provide useful dosing information, e.g., "Take one tablet daily. See package insert for complete dosing information."

b. Provide labeling information for all three drug product bulk containers [ ].

c. Provide labeling information for the [ ] carton containing professional sample blister.

d. Submit professional sample blister labels with the following revisions.

   i. In the front, use the same description, font, and size for proprietary and USAN names.
   ii. Indicate areas for lot number and expiration date.
   iii. In the back, add proprietary name. Revise dosage statement as recommended in comment 3aii above.

If you have questions about the contents of this facsimile, please contact Christine Yu at 301-827-1051.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Yu
9/13/04 04:30:02 PM
CSO

9/10/04

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #	21-704 (original)
Trade Name:	Allegra-D 24 hour Extended Release tablets
Generic Name:	Fexofenadine hydrochloride 180 mg/pseudoephedrine HCL 240 mg ER
Strengths:	180 mg/240mg
Applicant:	Aventis Pharmaceuticals, Inc.
Date of Application:	19 December 2003
Date of Receipt:	19 December 2003
Date clock started after UN:	N/A
Date of Filing Meeting:	3 February 2004
Filing Date:	17 February 2004
Action Goal Date (optional):	5 October 2004 User Fee Goal Date: 19 October 2004
Indication(s) requested:	Once daily relief of symptoms associated with SAR with nasal congestion in adults and children 12 years of age and older.

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA √
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S √ P _____
Resubmission after a withdrawal? No Resubmission after a refuse to file? No
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) _____

User Fee Status: Paid √ ***supplement fee*** Waived (e.g., small business, public health) ____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: (YES) NO
User Fee ID # 4443
Clinical data? YES √ Referenced to NDAs # 20-625, 20-872, 20-786, 20-021 NO _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

(YES) NO

If yes, explain:
Aventis has pediatric use marketing exclusivity that expires 11/12/2006.
Alza has NDA 20-021 patent until March 14, 2006.

Does another drug have orphan drug exclusivity for the same indication? YES (NO)

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES (NO)
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? (YES) NO
- Was form 356h included with an authorized signature? (YES) NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? (YES) NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A (YES) NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Entire submission is electronic. Required certifications were submitted in paper.
  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A (YES) NO

  Is it an electronic CTD? N/A YES (NO)
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  CMC section only is in CTD format. Entire NDA is electronic.
  Additional comments: ***Hybrid submission.***
- Patent information included with authorized signature? (YES) NO
- Exclusivity requested? YES, _____years (NO)
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? (YES) NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure information included with authorized signature? (YES) NO
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? (YES) NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? (YES) NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: Yes.

- End-of-Phase 2 Meeting(s)? Date(s) 1/29/02 under IND 48,486
  If yes, distribute minutes before filing meeting. DFS

- Pre-NDA Meeting(s)? Date(s) 8/27/03 under IND 66,289
  If yes, distribute minutes before filing meeting. DFS

Project Management

- Package insert consulted to DDMAC? N/A (YES) NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? (YES) NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  (N/A) YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  (N/A) YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of !Surveillance, Research and Communication Support?
  (N/A) YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? (N/A)

Chemistry

- Did applicant request categorical exclusion for environmental assessment? (YES) NO
  For pseudoephedrine
  If no, did applicant submit a complete environmental assessment? (YES) NO
  For fexofenadine
  If EA submitted, consulted to Nancy Sager (HFD-357)? (N/A) YES NO
  Not necessary per chemist based on assessment.
- Establishment Evaluation Request (EER) submitted to DMPQ? (YES) NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: *NDA 20-625, 20-872, 20-786, 20-021*

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
  This application requests approval of a once daily dosage of fexofenadine and pseudoephedrine.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES (NO)

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). Under review, not intentional

  YES (NO)

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES (NO)

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  __✓__ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  __✓__ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES (NO)

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES (NO)

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A (YES) NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).? ***See background information at the end of this review.***

    N/A YES (NO)

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    YES, IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  (YES) NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 3, 2004

BACKGROUND:
Aventis is seeking approval of a new fexofendine 180 mg/pseudoephedrine 240 mg extended release tablet to be taken once daily. At the EOP2 meeting on 1/29/02, the Division requested that Aventis submit a new NDA, versus submitting an efficacy supplement, because this extended release tablet [redacted] (similar to Sudafed 24), unlike the Allegra-D tablet (approved for twice daily dosing). The Office of Regulatory Affairs (User Fee staff) has been notified of this administrative "split" from an efficacy supplement and that the NDA has been submitted. Aventis has paid the supplement fee.

On a separate issue, although NDA 20-786 for Allegra-D (fexofenadine 60 mg/pseudoephedrine 120mg) extended release tablet, approved 12/24/1997, was not processed as a 505b(2) application, NDA 21-704 will be processed as a 505b(2) application. Aventis has submitted an amendment to the NDA with patent 2 and 3 certifications to address this status but has noted that they do not agree with 505b(2) designation. [The initial NDA was submitted as a 505b(1)].

Kim Colangelo, of the Office of New Drugs, has been notified of this b(2) application.

ATTENDEES:

DPADP- Christine Yu
Edwin Jao, Richard Lostritto
Joseph Sun
Sayed Al Habet, Tayo Fadiran
Charles Lee, Lydia Gilbert-McClain, Badrul Chowdhury

ASSIGNED REVIEWERS:

Discipline	
Medical:	Charles Lee
Secondary Medical:	Lydia Gilbert-McClain
Statistical:	
Pharmacology:	Lawrence Sancilio Joseph Sun
Statistical Pharmacology:	
Chemist:	Edwin Jao Richard Lostritto
Environmental Assessment (if needed):	
Biopharmaceutical:	Shinja Kim Emmanuel Fadiran
Microbiology, sterility:	
Microbiology, clinical (antimicrobial DP only):	
Regulatory Project Manager:	Christine Yu
DSI:	Sent

Other Consults: DMETS: Sent DDMAC: Sent

Per reviewers, are all parts in English or English translation? (YES) NO
If no, explain:

CLINICAL FILE √ REFUSE TO FILE ____

- Clinical site inspection needed: YES (NO)
- Advisory Committee Meeting needed? YES, date if known ____ (NO)

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

(N/A) YES NO

CLINICAL MICROBIOLOGY FILE ____ REFUSE TO FILE ____ (N/A)

STATISTICS FILE ____ REFUSE TO FILE ____ (N/A)

BIOPHARMACEUTICS FILE √ REFUSE TO FILE ____

- Biopharm. inspection needed: (YES) NO

PHARMACOLOGY FILE √ REFUSE TO FILE ____

- GLP inspection needed: YES (NO)

CHEMISTRY FILE √ REFUSE TO FILE ____

- Establishment(s) ready for inspection? (YES) NO
- Microbiology (N/A) YES NO

ELECTRONIC SUBMISSION:
Any comments: in good order

REGULATORY CONCLUSIONS/DEFICIENCIES:

____ The application is unsuitable for filing. Explain why:

√ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

____ No filing issues have been identified.

✓ Filing review issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Christine Yu, R.Ph.
Regulatory Project Manager, HFD-570

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/s/

Christine Yu
9/10/04 12:23:36 PM
CSO

Sandra Barnes
9/23/04 01:50:29 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: August 6, 2004

To: Kimberly S. Stranick, Ph.D. Director, US Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6317	**Fax number:** 301-827-1271
Phone number: 908-304-6580	**Phone number:** 301-827-1051
Subject: NDA 21-704 Allegra-D 24 Hour Notification of DMF Deficiency	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: ☐ YES √ NO

We refer to your NDA 21-704 for Allegra-D 24 Hour Extended-Release tablets.

The following comment pertains to [ ] carbon pouch in DMF [ ]

The DMF is inadequate to support your NDA. A letter will be sent to the DMF holder under a separate cover. Contact the DMF holder to discuss any deficiencies or clarifications.

If you have questions about the contents of this facsimile, please contact Christine Yu at 301-827-1051.

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/s/

Christine Yu
8/6/04 12:43:21 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2004

To: Kimberly S. Stranick, Ph.D. Director, US Regulatory Affairs	**From:** Christine Yu, R.Ph Regulatory Management Officer
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6317	**Fax number:** 301-827-1271
Phone number: 908-304-6580	**Phone number:** 301-827-1051

Subject: NDA 21-704 CMC Information Request

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES √ NO

Please refer to NDA 21-704 dated December 19, 2003, for Allegra-D 24 hour Extended –Release Tablets. We have the following request for information. (Your efforts for a prompt response will be appreciated.)

1. The following comments pertain to the pseudoephedrine HCl [ ]

   a. Provide an explanation as to why all three NDA stability batches are below label claim [ ]

   b. Provide an explanation [ ]

   c. Provide information about the container closure system for bulk pseudoephedrine HCl [ ]: shipped from [ ] to Aventis, MO.

   d. Provide acceptance criteria used by Aventis in receiving pseudoephedrine HCl [ ] instead of HPLC, should be used for — testing.

   e. Establish holding time for pseudoephedrine HCl [ ] based on appropriate stability testing data. Drug product expiry may depend on the outcome of the investigation.

2. The following comments pertain to the fexofenadine [ ]

   Until the — method is instituted for — testing of the finished drug product, we recommend that you add — testing of the fexofenadine [ ]

3. The following comments pertain to drug product specifications:

   a. Revise the acceptance criteria [ ]; to be reflective of the data:

	Proposed	Release data	Suggested
[ ]			]
[ ]			]

b. Revise the acceptance criteria [:] of Fexofenadine HCl to be reflective of the data:

	Release data (all batches)	proposed criterion	e.g. revised criterion	stability data (all batches, all conditions)	Proposed criteria	Suggested e.g. criteria
Total	[					]

c. Provide an explanation of [ ] demonstrated in Figure 1 to 4 and figure 23-54.

4. The following comments pertain to stability and expiry dating of the drug product:

a. The moisture content in all trade packages and bulk containers display an upward trend (although still within specification) during stability testing, and more so for [ ] blister and bulk containers. Provide evidence that the drug product stored in the proposed bulk containers to the proposed maximum storage time can still be stored in the proposed trade packages to the balance of the proposed expiry dating. Otherwise, the expiry dating can only be determined based on the data and appropriate extrapolation under the worst case scenario (e.g., the least protective package).

b. You have not provided data demonstrating that the carbon canisters have adequate activity and [ ] in the HDPE bottles and that the moisture does not [ ] stability testing. Therefore, monitor and report the [ ] HDPE bottles with and without the carbon canisters to prove efficacy of its intended use for the entire shelf life of the drug product.

5. The following comments pertain to the container/closure system:

Provide adequate information [ ] for two bulk storage containers: [ ] For each referenced DMF, provide LOAs with the location of most current and relevant information, i.e., section, page, and date of letter.

6. The following comment pertains to labeling:

Provide labeling information for bulk packaging [ ] blisters.

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/s/

Christine Yu
7/15/04 05:08:00 PM
CSO

7/1/04

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:** May 7, 2004	**ODS CONSULT #:**
February 24, 2004	**PDUFA DATE:** October 19, 2004	04-0074

TO: Badrul Chowdhury, M.D.
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Christine Yu, R.Ph.
Project Manager, Division of Pulmonary and Allergy Drug Products
HFD-570

PRODUCT NAME:	**NDA SPONSOR:**
Allegra-D 24 Hour™ (Fexofenadine HCl and Pseudoephedrine HCl Extended-release Tablets) 180 mg/240 mg **NDA#:** 21-704	Aventis Pharmaceuticals, Inc.

SAFETY EVALUATOR: Scott Dallas, R.Ph.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, "Allegra-D 24 Hour™" provided the sponsor adds an appropriate modifier (e.g., 12 Hour) to the proprietary name, Allegra-D (NDA 20-786) prior to the launch of Allegra-D 24 Hour™ to further differentiate these products.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

3. DDMAC finds the proprietary name, "Allegra-D 24 Hour™" acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 15, 2004

NDA NUMBER: 21-704

NAME OF PRODUCT: **Allegra-D 24 Hour™**
(Fexofenadine HCl and Pseudoephedrine HCl Extended-release Tablets)
180 mg/240 mg

NDA SPONSOR: **Aventis Pharmaceuticals, Inc.**

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products for an assessment of the proposed proprietary name, Allegra-D 24 Hour™. Container labels and package insert labeling were provided for review and comment.

PRODUCT INFORMATION
Allegra-D 24 Hour™ is a combination product of fexofenadine hydrochloride and pseudoephedrine hydrochloride. Fexofenadine hydrochloride is an antihistamine with selective peripheral H_1-receptor antagonist activity and pseudoephedrine hydrochloride is a sympathomimetic amine. Each Allegra-D 24 Hour™ tablet contains 180 mg of fexofenadine hydrochloride and 240 mg pseudoephedrine hydrochloride. The combination is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. The recommended dose of Allegra-D 24 Hour™ is one tablet once daily administered before a meal.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Allegra-D 24 Hour™" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.
[3] The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Allegra-D 24 Hour™". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, "Allegra-D 24 Hour™", acceptable from a promotional perspective.

2. The Expert Panel did not identify any proprietary names that were thought to have the potential for sound or look-alike confusion with "Allegra-D 24 Hour™", except the proprietary names Allegra and Allegra-D. These products are listed in Table 1 (see below), along with the dosage form available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Established name, Dosage form(s), and Strength(s)**	**Usual adult dose***	**Other****
Allegra-D 24 Hour™	**Fexofenadine HCl and Pseudoephedrine HCl Extended-Release Tablets, 180 mg/240 mg**	**Take 1 tablet daily.**	
Allegra	Fexofenadine HCl, Tablets, 30 mg, 60 mg, and 180 mg Capsules, 60 mg	Adults and children 12 years of age and older: Take 60 mg twice daily or 180 mg once daily.	SA/LA
Allegra-D	Fexofenadine HCl and Pseudoephedrine HCl Extended-Release Tablets, 60 mg/120 mg	Take 1 tablet twice daily.	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

[4] WWW location http://www.uspto.gov/main/trademarks.htm

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The Expert Panel (EPD) discussed all names identified in POCA that were considered to have significant phonetic or orthographic similarities to Allegra-D 24 Hour™.

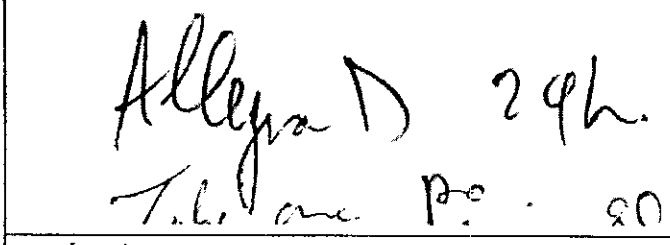
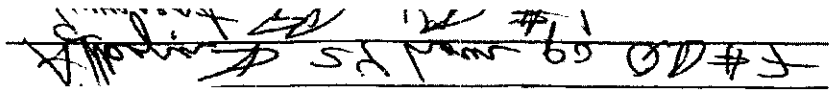
C. ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database for any post-marketing safety reports of medication errors involving "Allegra", and "Allegra-D". The MedDRA Preferred Term (PT) "Medication Error", the tradenames, and verbatim for "Alleg%" and "Fexofe%" were used to perform the searches. The search revealed that there was some potential confusion due to the look-alike labeling of the Allegra product line. There was a report of an actual error, in which Allegra tablets, 60 mg, were dispensed instead of Allegra capsules, 60 mg. Additionally, the search revealed that there was confusion and an actual medication error due to scripted look-alike similarities of the proprietary names Allegra-D and Allerx-D. The search also revealed two actual errors due to the potential for the proprietary name Allegra to sound and or look similar to the proprietary name Viagra. There was one report of potential confusion due to the look-alike similarities between Allegra capsules and Actigall capsules, and because both products have the potential to be stored in close proximity to each other. DMETS will continue to monitor post-marketing error reports involving Allegra, Allegra-D and these other products.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of "Allegra-D 24 Hour™" with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses) for the proposed proprietary name. These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Allegra-D 24 Hour™". These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via email. In addition, outpatient orders were recorded on voice mail and included an order for "Allegra-D 24 Hour™". The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: 	*Outpatient:* Allegra-D 24 Hour Take one po qd Number 30
Inpatient: 	

2. Results:

   One participant in the written inpatient prescription study interpreted the proposed name as Allegra 24 hr. A total of twelve participants in the inpatient and outpatient prescription studies interpreted the proposed name as Allegra D and did not include the modifier "24 hour". See Attachment A for the complete listing of interpretations from the verbal and written prescription studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Allegra-D 24 Hour™", the primary concerns related to look-alike and sound-alike confusion with Allegra and Allegra-D. Additionally, no names of concern were identified using POCA. DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that the proposed name, Allegra-D 24 Hour™, could be confused with Allegra and Allegra-D. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Look-alike and Sound-alike Concerns

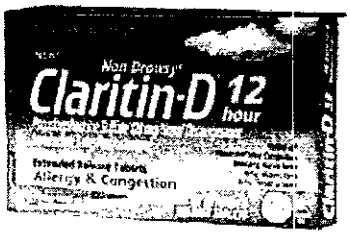
   DMETS acknowledges that the current accepted practice is to add an appropriate suffix to an existing proprietary name in order to create a unique proprietary name for a new modified release dosage formulation of a medication. Although the addition of a modifier has been an accepted practice to identify a new modified dosage formulation, it has not been a perfect system. In this case the sponsor has proposed to add the modifier "24 Hour" to the proprietary name "Allegra-D". If approved this would create a product line with three proprietary names, Allegra, Allegra-D, and Allegra-D 24 Hour™. It would also create a product line in which each subsequent proprietary name is longer than the previously approved proprietary name. Therefore, DMETS is concerned that increasing the length of the proprietary name would increase the risk that the modifier is omitted from the proprietary name. If the modifier, 24 Hour, is omitted, then the product

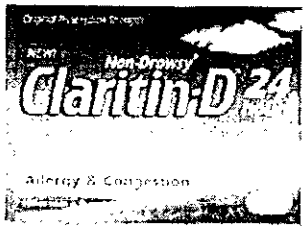
will be confused with the product Allegra-D. Medication prescribing practices indicate that healthcare professionals will abbreviate (e.g., HCTZ for hydrochlorothiazide) and or even omit parts of the proprietary name (e.g., Z-Pak for Zithromax Z-Pak), if the healthcare professional believes the identity of the product has been safely communicated. Therefore, if healthcare professionals do not fully understand the importance of the modifier "24-Hour", then healthcare professionals may not include the modifier on an order. As previously stated if the modifier, 24 Hour, is not communicated, then the intended product, Allegra-D 24 Hour™ would be communicated as Allegra-D. Post-marketing error reports and independent research has indicated that the omission of modifiers continues to cause medication errors. Timothy S. Lesar, Pharm.D, conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms.[6] Detailed analysis of 402 medication errors over a 16 month period (Sept. 1999 to Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled release dosage formulation (280 cases or 69.7%). Studies such as this one, support DMETS concern that healthcare professionals may fail to include the modifier, "24 Hour", on a prescription. Errors due to the omission of the modifier, 24 Hour, would be very difficult to detect since the order would correctly identify the product, Allegra-D, and the directions for use could be written as "Take one tablet daily" for both products. Therefore, it is very important that healthcare professionals and consumers are educated about differences between the two different antihistamine/decongestant combination products, and the importance of including the modifier "24 Hour" to identify the "Allegra-D 24 Hour" product.

In order to further differentiate the products, Allegra-D and Allegra-D 24 Hour, DMETS believes an appropriate modifier such as "12 Hour" should be associated with Allegra-D (NDA 20-786). This would create proprietary names, in which the modifiers would identify the normal dosing schedule for that product. The addition of a modifier to Allegra-D, would also eliminate the use of the proprietary name Allegra-D, since Allegra-D would no longer identify a specific product. The significance of this additional modifier would be to prevent errors in which the omission of the modifier, 24 Hour, on an order could be interpreted as Allegra-D. If a modifier were required to identify both medications, then any modifier omission would alert the listener or reader that the order was incomplete. Therefore, healthcare professionals and consumers must be educated to understand that the modifiers, "12 Hour" and "24 Hour", are significant and necessary to correctly identify a specific product.

The modifiers "12 Hour" and "24 Hour" are already being used to differentiate two loratadine/pseudoephedrine sulfate medications for the product line extension of Claritin. DMETS has not received any post-marketing error reports involving confusion between the products Claritin-D 12 Hour and Claritin-D 24 Hour. Examples of the carton labels for Claritin-D 12 Hour and Claritin-D 24 Hour are included for review (see page 7).

[6] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.





Therefore, DMETS recommends that proactive measures be taken before the launch of the second fexofenadine HCl/pseudoephedrine HCl dosage formulation is approved for distribution in the marketplace, to add the modifier "12 Hour" to the proprietary name of Allegra-D. The use of the modifiers "12 Hour" and "24 Hour" should help to further differentiate Allegra-D from Allegra-D 24 Hour.

2. Introduction of a New Dosage Formulation into the Marketplace

Post-marketing medication error reports indicate that healthcare professionals may be uninformed that a new dosage formulation is available and therefore continue to make medication errors months after the distribution date (not the approval date) of a new dosage formulation. By examining medication error reports submitted to the FDA, it becomes evident that a long period of time may be required for healthcare professionals to learn that a new dosage formulation has been marketed. One such example involved the extension of the Metadate product line. Metadate ER 20 mg, a methylphenidate product with a twice a day dosing frequency was approved on June 1, 1988. Then the product line was extended with the approval of Metadate CD 20 mg on April 3, 2001, a methylphenidate product with a once daily dosing frequency. The distribution of this second product, Metadate CD began on November 15, 2001. One medication error report submitted to the FDA involved a pharmacist who dispensed Metadate ER to 3 patients on 6 occasions, [January 02, February 02 (2x), March 02, and April 02 (2x)], instead of Metadate CD, because the pharmacist was unaware of the new product. The report also states that the pharmacist discovered this error after reading a newsletter that contained excerpts on errors involving these two products. Therefore, this pharmacist did not discover a new dosage formulation was available until after the product had been in distribution for 6 months, or one year after the approval date of the product. Thus DMETS also recommends that the sponsor conduct a comprehensive education campaign prior to and during the introduction of this new dosage formulation into the marketplace (see Section III below).

If the Division agrees with DMETS that an appropriate modifier, (e.g., 12 Hour) should be added to the proprietary name, Allegra-D (NDA 20-786) to further differentiate Allegra-D and Allegra-D 24 Hour, then educating healthcare professionals and consumers becomes very important. If the name Allegra-D is changed to Allegra-D 12 Hour, then there will be 3 proprietary names and labeling in the marketplace for two

different products. Pharmacists could conceivably have containers for Allegra-D, Allegra-D 12 Hour, and Allegra-D 24 Hour on their pharmacy shelf at the same time, and at the same time receive prescriptions written by physicians as "Allegra-D, one tablet daily". Healthcare professionals and consumers must be educated that Allegra-D 12 Hour will be the new name for Allegra-D, and that there has been no change in this dosage formulation. Healthcare professionals and consumers must be educated that a new dosage formulation containing more fexofenadine HCl and pseudoephedrine HCl will be marketed under the proprietary name, Allegra-D 24 Hour. Also that the modifiers, 12 Hour and 24 Hour, identify the normal dosing frequency for the product. Healthcare professionals must be educated that orders for Allegra-D do not clearly identify a specific product and that all orders for Allegra-D should be corrected to include the modifier 12 Hour or 24 Hour. During this transition period, it is extremely important for pharmacists and nurses to be educated that they must be vigilant for any orders communicated as "Allegra-D, Take one tablet daily". If a healthcare professional receives an order for Allegra-D, then the healthcare professional must be educated and instructed to contact the prescribing physician to clarify and correct the order. These are some of the issues that should be addressed in the comprehensive education campaign prior to and during the introduction of the new dosage formulation and proprietary names into the marketplace.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container label, and package insert labeling of Allegra-D 24 Hour™, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABELS

   a. Increase the prominence of the proprietary name, Allegra-D 24 Hour™.

   b. [redacted]

   c. DMETS recommends that the "Rx only" statement be relocated to the principal display panel.

   d. DMETS recommends that the "Dosage and Administration" statement provide useful dosing information, since a specific and usual dose is recommended for this product in the package insert labeling. (e.g., Usual dose: Take one tablet daily. See package insert for complete dosing information.)

2. CARTON LABELING

   No carton labeling was available at this time for comment.

3. PACKAGE INSERT LABELING

   DMETS has no comments at this time.

4. EDUCATION

Post-marketing experience indicates that medication errors occur when healthcare professionals are unaware that a new modified dosage formulation of a medication has been introduced into the marketplace. Therefore, DMETS recommends the sponsor conduct an education campaign prior to and during the introduction of this product into the marketplace. Also if an appropriate modifier (e.g., 12 Hour) is added to the proprietary name of Allegra-D, then the education campaign should address the transitional period when there would be three proprietary names (e.g., Allegra-D, Allegra-D 12 Hour, and Allegra-D 24 Hour) for two different drug products. The education campaign should alert all healthcare professionals concerning the need to include a modifier on all orders, the differences between the products within the Allegra product line, and how to safety prescribe the products in order to prevent medication errors.

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Allegra-D 24 Hour™" provided the sponsor adds an appropriate modifier (e.g., 12 Hour) to the proprietary name, Allegra-D (NDA 20-786) prior to the launch of Allegra-D 24 Hour™ to further differentiate these products.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

3. DDMAC finds the proprietary name, "Allegra-D 24 Hour" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/S/

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

Concur: /S/

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A:

Prescription Study Results for the proposed name "Allegra-D 24 Hour"

Inpatient Written	Outpatient Written	Voicemail
Allegra 24 hr	Allegra D	Alegra d 24 h
Allegra D	Allegra D	Allegra D 24 Hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D	Allegra D 24 hour
Allegra D	Allegra D 24 h	Allegra D 24 hr
Allegra D - 24 Hour	Allegra D 24 Hour	Allegra D 24 hr
Allegra D 24	Allegra D 24 hour	Allegra D 24 hr
Allegra D 24 hour	Allegra D 24 Hour	Allegra D 24-Hour
Allegra D 24 hour	Allegra D 24 hour	Allegra D 24-hour
Allegra D 24 hour	Allegra D 24 hr	Allegra D24 hours
Allegra D 24 hour	Allegra D 24H	Allegra-D 24 hour
Allegra D 24 hour	Allegra D 24h	Allegra-D 24 hour
Allegra D 24 hour	Allegra D 24h	Allegra-d 24 hour
Allegra D 24 hour	Allegra D 24h	Allegra-D 24 Hour
Allegra D 24 Hour	Allegra D 24H	Allegra-D 24 hour
Allegra D 24 hours	Allegra D 24 h	Allegra-D 24 hr
Allegra D 24 hr	Allegra-D 24 hour	Allegra D 24hour
Allegra D 24-hour	Allergra D 24h	
Allegra ID		
Allegra-D 24 Hour		
Allegra-D 24 hour		
Allergan D 24 hour		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Scott Dallas
7/1/04 01:08:04 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/1/04 02:46:20 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/1/04 02:58:12 PM
DRUG SAFETY OFFICE REVIEWER

KB for BC 3/3/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
Division of Drug Marketing, Advertising and Communications, HFD-42 **PKLN Room 17b-17**	Christine Yu, R.Ph. Division of Pulmonary & Allergy Drug Products, HFD-570

	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4 March 2004		21-704	Original NDA	19 December 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Allegra-D 24 hour ER tablet (fexofenadine 180 mg/ pseudoephedrine 240mg)	Standard	3	30 June 2004

NAME OF FIRM: Aventis Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please perform DDMAC review of original NDA 21-704. Entire application is electronically available in EDR. Please contact me if you have any questions at 827-1051.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-704

3/2/04

Aventis Pharmaceuticals, Inc.
200 Crossing Blvd.
P.O. Box 6890
Bridgewater, NJ 08807-0890

Attention: Kimberly S. Stranick, Ph.D.
Director, Regulatory Liaison
U.S. Regulatory Affairs

Dear Dr. Stranick:

Please refer to your December 19, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) 24 hour Extended Release tablet.

We also refer to your submission dated February 17, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 17, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

> At the End-of-Phase II meeting held January 29, 2002, under IND 48,486, we had recommended that you study the effects of grapefruit and apple juices on fexofenadine bioavailability. Provide information from or about the status of this/these study(ies).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Our facsimile correspondence requesting additional Chemistry, Manufacturing and Controls (CMC) information to facilitate our review was sent February 13, 2004.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
3/2/04 03:57:01 PM

2/24/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 KLN Rm. 6-34	Christine Yu, R.Ph. Regulatory Project Manager, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
24 February 2004		21-704	Original NDA	19 December 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Allegra-D 24 hour ER tablet (fexofenadine HCl 180 mg/ pseudoephedrine HCl 240 mg)	Standard	Standard	30 June 2004

NAME OF FIRM: Aventis Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ **OTHER *(SPECIFY BELOW)*:**

Trade name review

II. BIOMETRICS

TICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
E A OR B NDA REVIEW ND OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Entire submission available in EDR.

PDUFA DATE: 10/19/04
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
NDA 21-704
570/RPM/C Yu

URE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

February 17, 2004

Badrul Chowdhury, M.D., Ph.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products (HFD-570)
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20857

NDA AMENDMENT
NDA 21-704
ALLEGRA-D 24 HOUR™ Extended Release Tablets

Dear Dr. Chowdhury:

Reference is made to NDA 21-704 ALLEGRA-D 24 HOUR™ (fexofenadine hydrochloride 180mg and pseudoephedrine hydrochloride 240mg) Extended-Release Tablets submitted to the Agency on December 19, 2003 seeking approval for ALLEGRA-D 24 HOUR to be administered once daily for the relief of symptoms associated with seasonal allergic rhinitis with nasal congestion in adults and children 12 years and older. Reference is also made to a telephone conversation between the undersigned and Ms. Christine Yu, Regulatory Management Officer, Division of Pulmonary & Allergy Drug Products, which took place on February 6, 2004.

In that conversation, Ms. Yu advised that upon review of this application, the Agency had determined that this NDA would be considered under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Additionally, Ms. Yu requested that Aventis provide by February 17, 2004 appropriate patent certification(s) pursuant to 21 CFR §314.50(i)(1)(i)(A).

Aventis does not agree with the Agency's designation of this NDA as a type 505(b)(2) application, and respectfully reserves the right to revisit this issue or challenge this determination in future. However, in order to maintain the user fee goal date for the Agency's review of this application, Aventis submits the enclosed certification documentation for Item 14 of NDA 21-704. Aventis respectfully reserves the right to submit revised certifications for this application.

200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

Aventis considers the information included in this submission to be confidential and proprietary, and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis Pharmaceuticals according to CFR §314.430.

On behalf of Aventis Pharmaceuticals, we look forward to continuing to work with the Division to facilitate the review of this application. If you have any questions or need additional information during the review, please contact the undersigned, Kimberly S. Stranick, Ph.D., at (908) 304 6580 or. in my absence, Eric A. Floyd, Ph.D., at (908) 231 2474.

Sincerely,

Kimberly Stranick

Kimberly S. Stranick, Ph.D.
Director, Regulatory Liaison
US Regulatory Affairs

Attachment

Enclosures:
Electronic archival copy: 1 CD-ROM labeled *NDA 21-704 ALLEGRA-D 24 HOUR™ Extended Release Tablets AMENDMENT February 17, 2004*
1 paper copy of Cover Letter, Form 356h and certifications in Items 14 with original signatures

cc: Ms. Christine Yu, Regulatory Project Manager (via fax)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 13, 2004

To: Kimberly S. Stranick, Ph.D. Director, US Regulatory Affairs	**From:** Christine Yu, R.Ph. Regulatory Management Officer
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6317	**Fax number:** 301-827-1271
Phone number: 908-304-6580	**Phone number:** 301-827-1051

Subject: NDA 21-704 Allegra-D 24 hour
Request for CMC information

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES √ NO

We refer to your original NDA 21-704 submitted December 19, 2003. We note that you have provided cross references to approved NDAs, supplements, and annual reports for the Chemistry, Manufacturing and Controls portions of your application. In order to facilitate the review of your NDA, please provide the following information:

1. The name, location, contact persons, current status, and CFN numbers of all the current manufacturers/suppliers, packagers, and testers of **Fexofenadine HCl**.

2. The Drug Master File (DMF) numbers and Letters of Authorization (LOAs) from the above manufacturers/suppliers.

3. The most current approved specifications with all acceptance criteria.

If you have questions about the contents of this facsimile, please contact Ms. Christine Yu at 301-827-1051.

1/14/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-704

Aventis Pharmaceuticals, Inc.
200 Crossing Blvd.
P.O. Box 6890
Bridgewater, NJ 08807-0890

Attention: Kimberly Stranick, Ph.D.
Director, Regulatory Liaison

Dear Dr. Stranick:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Allegra-D 24 hour (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) Extended Release tablet
Review Priority Classification:	Standard (S)
Date of Application:	December 19, 2003
Date of Receipt:	December 19, 2003
Our Reference Number:	NDA 21-704

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 19, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary & Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

December 1, 2003

Mellon Bank
Three Mellon Bank Center
27th floor
(FDA 360909)
Pittsburgh, PA 15259-0001

RE: User Fee for M016455/ fexofenadine HCl 180mg + pseudoephedrine HCl 240mg
NDA # 21-704 (N021704)

To whom it may concern:

Please find enclosed the User Fee payment in the amount of $286,750.00 for the upcoming ALLEGRA-D 24 HOUR™ (M016455 / fexofenadine HCl 180mg + pseudoephedrine HCl 240mg) Extended-Release Tablet NDA submission. The User fee ID No. for this submission is 4645.

If you have any questions or if I can be of further assistance, please contact me.

Sincerely yours,

Eric A. Hoyl for S.C.

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs
Tel (908) 231 5863 or (908) 304 6580

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Aventis Pharmaceuticals, Inc.
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

2. TELEPHONE NUMBER *(Include Area Code)*

(908) 304-6580

3. PRODUCT NAME

Fexofenadine Hydrochloride (INN) 180 mg and Pseudoephedrine Hydrochloride (INN) 240 mg - ALLEGRA-D 24 HOUR(TM)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021704

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4645 (assigned 11 November 2003)

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Steve Caffe, MD Head, US Regulatory Affairs	12/01/2003

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

Memorandum of Telephone Facsimile Correspondence

Date: September 25, 2003

To: Kimberly S. Stranick, Ph.D.
Director, U.S. Regulatory Affairs

Fax: 908-304-6317

From: Christine Yu, R.Ph.
Regulatory Management Officer

Subject: IND 66,289 for fexofenadine HCl/pseudoephrine HCl 24-hour ER tablets
Minutes of August 27, 2003 pre-NDA meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on August 27, 2003. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

MEETING MINUTES

DATE:	August 27, 2003
TIME:	10:30 AM - 12:00 PM
APPLICATION:	IND 66,289
TYPE:	Pre-NDA meeting
DRUG NAME:	Fexofenadine HCl/pseudoephrine HCl 24-hour ER tablets
INDICATION:	Relief of symptoms associated with SAR in adults and children 12 years and older
IMTS#:	10791
SPONSOR:	Aventis Pharmaceuticals, Inc.
Represented by:	Eric Floyd, Regulatory Affairs Kimberly Stranick, Regulatory Affairs Madhu Anant, Regulatory Affairs Stephen Sherman, Aventis- Canada John Gigantino, Regulatory CMC Rosemary Crew, Regulatory Operations Ian Davidson, Project Team Leader Prafulla Agrawala, Global Project Development Rajiv Haribhakti, Global Project Development Kazimierz Chrzan, Global Project Development Doug Hatzenbuhler, Global Project Development Barbara Kittner, Clinical Sriram Krishnaswami, Drug Metabolism/Pharmacokinetics Abdul Sankoh, Biostatistics
FDA attendees:	Division of Pulmonary & Allergy Drug Products, HFD-570 Brian Rogers, CMC Reviewer Edward Jao, CMC Reviewer Guirag Poochikian, CMC Team Leader Shinja Kim, Clinical Pharmacology & Biopharmaceutics (CPB) Reviewer Emmanuel Fadiran, CPB Team Leader Feng Zhou, Biometrics Reviewer James Gebert, Biometrics Team Leader (Actg) Charles Lee, Medical Reviewer Lydia Gilbert-McClain, Medical Team Leader (Acting) Carol Bosken, Medical Reviewer Badrul Chowdhury, Director Christine Yu, Regulatory Management Officer Eric Duffy, Director, DNDC II, HFD-820

Aventis submitted a meeting request for a pre-NDA meeting on May 30, 2003, to discuss NDA submission strategy for the "Allegra-D 24 hour" product. Briefing packages for the meeting were dated July 25, 2003. End of Phase 2 meeting for the same product was held January 29, 2002.

Agenda (order based on the questions included in the briefing package)

Regulatory
Clinical Pharmacology & Biopharmacuetics (CPB)
Clinical
Chemistry, Manufacturing & Controls (CMC)

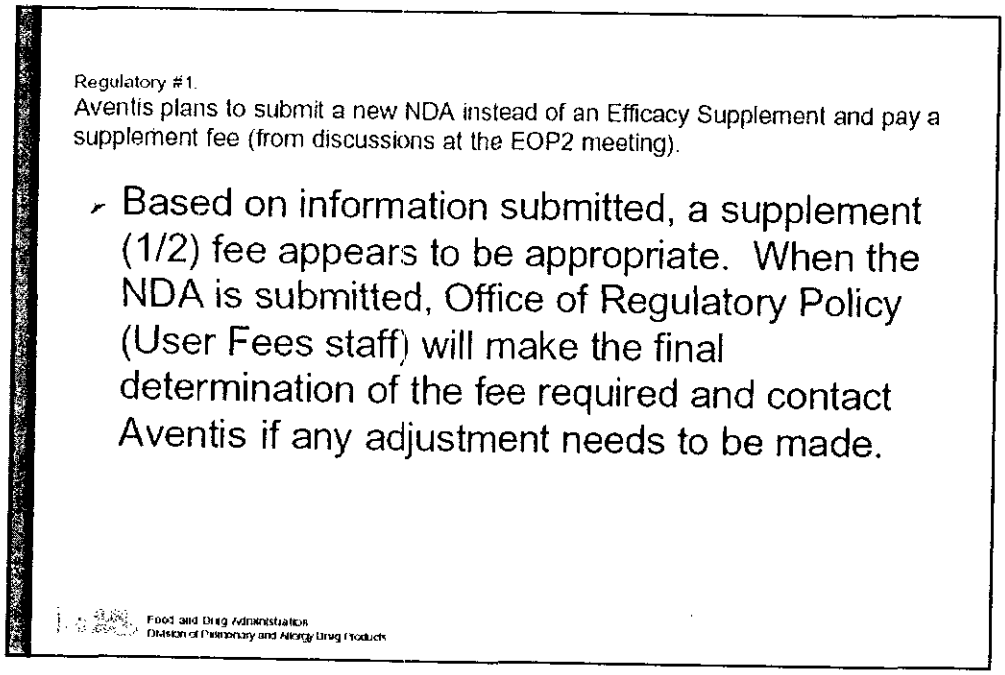
Guidances for Industry referenced during the meeting

Guidances represents the Food and Drug Administration's (FDA's) current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Minutes

The Division presented slides which included Aventis' questions, followed by the Division's responses. Discussions during the meeting are captured between the slides.

Regulatory



Regulatory #2:
The NDA will be prepared in the NDA / Common Technical Document (CTD) hybrid format. The CMC sections will be presented as CTD formatted Modules, while the remainder of the submission will follow 356h NDA format... Requesting comments on TOC...

- Table of contents is correct with the following exceptions / notations:
  - HUPHARM folder is indicated as standalone, it should be a sub-folder of HPBIO per IT3 Guidance of January, 1999, page 32.
  - Your 8G and 8H entries indicate a "Clinical" folder for the ISE and ISS. Both the ISE and ISS should be sub-folders of CLINSTAT – a typo?

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Regulatory #3:
Aventis intends to ... (sic) submit mixed (hybrid) submission consisting of an eNDA backbone and presentation for all *except CMC* which will be in the CTD module format...
...any specific recommendations or requests that will ease the review of this electronic submission?

- The Guidances pertaining to this type of submission (IT 3 of 01/1999 and the Guidance for Industry: Submitting Marketing Applications According to ICH-CTD Format... of August 2001, if followed, will fulfill all the requirements needed for review of this submission.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Regulatory #4
A Data Correction Form will be provided in the front of each CRF. (sic) They will be bookmarked, but, no hyperlink(s) will be provided for corrected items…
Does the Agency concur with this approach?

- Yes
  - Hyperlinks to corrected items are *suggested* in the IT3 of 1/1999, however, these are only suggested as a *means of avoiding confusion* and are not required.
- Locating the Data Correction Forms immediately preceding the appropriate CRF will suffice in minimizing confusion.

Regulatory #5
(sic) Aventis plans to submit CRF's for AE's, Serious AE's and Pregnancy only, with others available upon request…
Does the Agency concur?

- Yes

Regulatory #6
(sic) Referring to IT3, Aventis does not plan to include Patient Profiles…
Does the Agency concur with this plan?

- For this submission, no Patient Profiles are needed.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Regulatory #7
Aventis does not plan to submit any separate document(s) equivalent to Item 10 (Statistical) of the NDA. (sic) All data will be included with the study report (M016455S/100)
Does the Agency concur?

- This is perfectly acceptable according to the IT3 Guidance of 1/1999, providing proper entries and links are provided in the TOC Item #10 categories to this data.
- CPB, however, does have additional input concerning included data that will come later in this presentation.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Clinical Pharmacology & Biopharmaceutics

REGULATORY

7. Aventis does not plan to submit any separate document equivalent to the Item 10 (Statistical) of the NDA. All statistical information for the pivotal bioequivalence study (M016455S/1001) will be included with the study report. Does the Agency concur?

Comment: Also include statistical information for M016455S/1002 in the study report.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

CLINICAL PHARMACOKINETICS AND BIOAVAILABILITY

8. As discussed between the FDA and Aventis at the End of Phase II meeting, the clinical support for the approval of ALLEGRA-D 24 HOUR (fexofenadine 180 mg and pseudoephedrine 240 mg) Extended Release Tablets will be based on a pilot bioavailability study (KA467) with a prototype combination formulation, a pivotal single and multiple dose bioequivalence study (M016455S/1001) and an effect of food study (M016455S/1002) with the final combination formulation. Does the Agency concur?

Comment: We concur (CPB perspective).

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

9. In order to facilitate the pharmacokinetic/biostatistical review, the final concentration-time data from the pivotal BE study (M016455S/1001) will be submitted with a data description file according to electronic submission guidelines as SAS transport (.xpt) and .pdf files, respectively.

   Does the Agency have any other specific requests to ease the review?

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Comment:

- In addition to the PK parameters listed in Table 1 (page 127), obtain other PK parameters such as, T_{max} and $t_{1/2}$ for fexofenadine and PSE following a single dose (i.e., after the first dose administration) and at steady state, $C_{average}$ and degree of fluctuation (C_{max}-C_{min}/C_{av}), etc., for fexofenadine and PSE from the data M016455S/1001.
- Provide SAS transport (.xpt) and .pdf files for the data from Study M016455S/1002.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

10. Aventis proposes to set dissolution specifications for pseudoephedrine HCl from the ALLEGRA-D 24 HOUR tablet as described in Section 7 of this briefing package. Does the agency concur with the proposed approach?

Comment:

No. the IVIVC has to be externally validated before it can be used to set dissolution specification.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

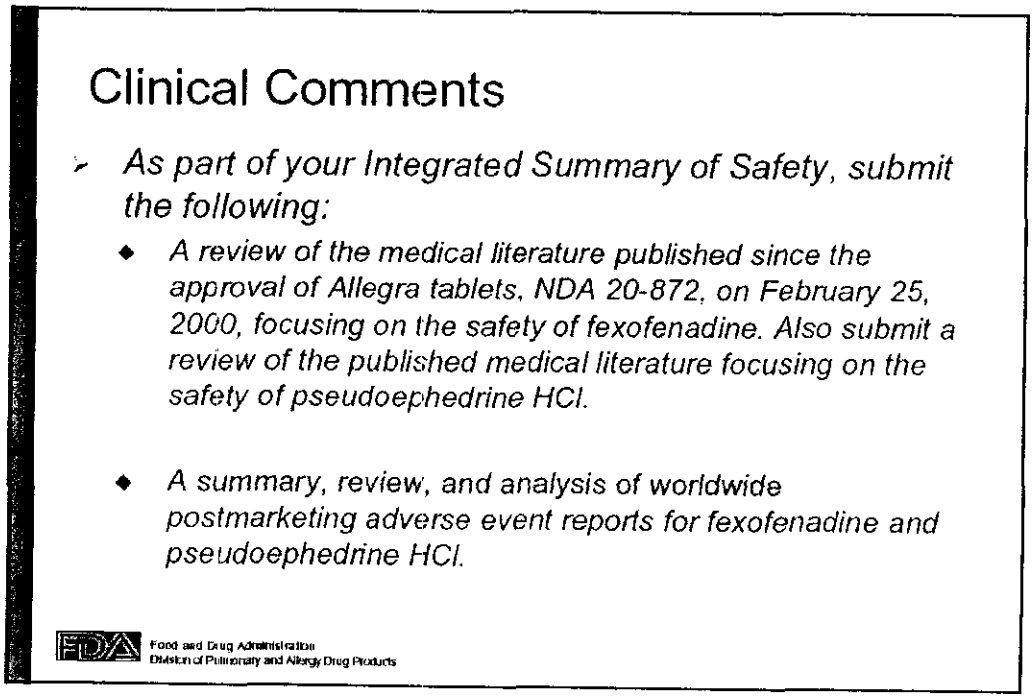
The Division referenced the Guidance for Industry entitled, "Extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations," and stated that the data from the fasted period of the food effect study may be used for the external validation of the IVIVC.

11. Fexofenadine HCl alone and in combination with pseudoephedrine HCl has been previously studied and relevant results of Phase I studies have been submitted to NDAs 20-265, 20-872 and 20-786. An overview of the results of these studies has been presented in this document in summary tables (Section 7.4, Summary Table of Completed Studies). Aventis proposes to include the same tables in the NDA and not include the full study reports. No additional Phase I studies beyond those already submitted are planned for the ALLEGRA-D 24 HOUR NDA. Does the Agency concur?

Comment: We concur.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Clinical comments



Post-meeting addendum-
In response to a post-meeting request from Aventis regarding the second bullet above and discussion at the meeting, the Division provides the following clarification.

> *Summary, review, and analysis of postmarketing adverse event reports for the currently marketed twice daily formulation of Allegra-D (fexofenadine 60 mg/pseudoephedrine 120 mg) tablets would provide the information needed for review of the NDA.*

On a separate note, Aventis stated that the adverse events data in the package insert will not be recoded from MMDWHO to MeDRA. This was acceptable to the Division.

Chemistry, Manufacturing and Controls

Question 12. Format and content of CMC documentation

See response for Regulatory question 2.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Question 13. Pseudoephedrine HCl Drug Substance Particle Size Effect on Dissolution

[ ]

Table 5.2.1- 1 Particle Size Description for Developmental and NDA Stability Batches

[ ]

The data from all these batches will be provided in the pharmaceutical development section of the NDA. The data demonstrate that particle size has no impact on dissolution properties as measured by the dissolution similarity factor f2 calculation. (Guidance for Industry; Immediate Release Solid Oral Dosage Forms, Scale-up and Post Approval Changes: Chemistry, Bioequivalence Documentation: (CDER November 1995). The comparison analysis for these batches w ll be presented in the NDA.

Does the Agency agree that this approach is acceptable for defining the particle size specification for pseudoephedrine HCl?

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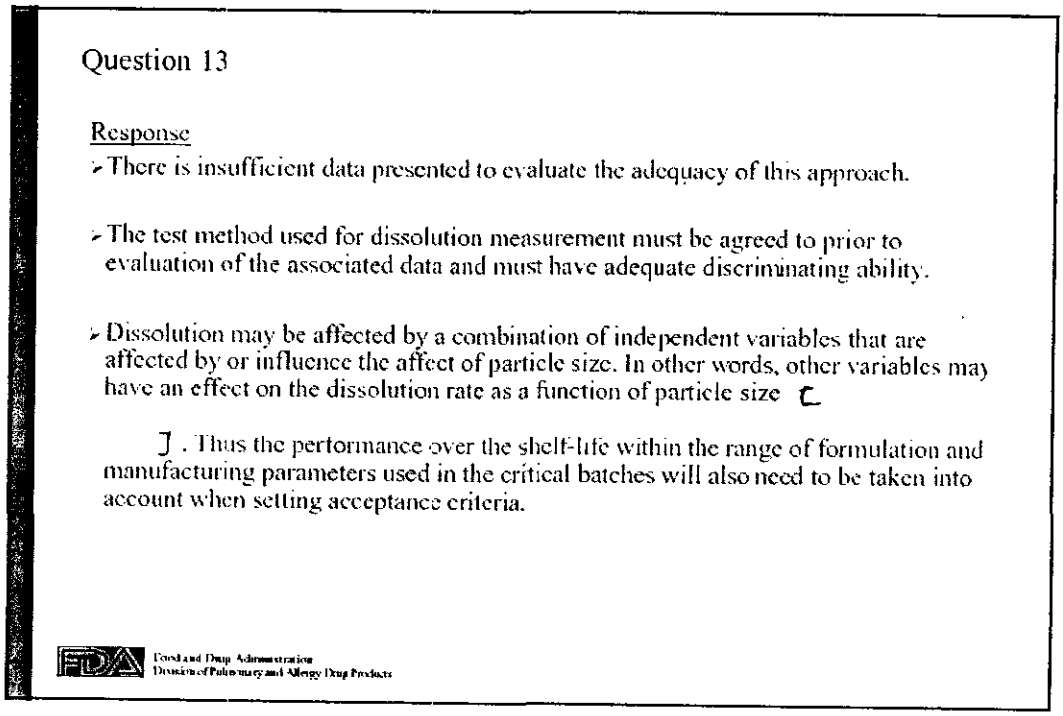

In response to the second bullet above, Aventis stated that they had found the dissolution test method to be adequately discriminating, but they will make sure to get the Agency's agreement on the method before evaluating the data.

The Division noted that agreement should be reached as soon as possible, preferably before the stability studies are initiated.

Question 13

Response (cont'd)

- Please explain the use of — batches of pseudoephedrine HCl in one batch of drug product. The utility of this approach is unclear.

- Please note that the SUPAC modified release guidance for solid oral dosage forms must be referenced for the appropriate comparison criteria and calculations.

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Regarding the first bullet in the slide above, Aventis replied that [redacted] Additionally, they stated that particle size of the drug substance did not affect dissolution. Although they will submit the data, release of particles were independent of PSE particle size. [redacted]

The Division noted Aventis rationale but recommended that the PSE particle size still be constrained to a reasonable range.

Question 14. In-Process Tests for Commercial Product

[

]

Does the Agency agree with this proposal?

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Question 14

Response

The proposed in-process testing may be adequate if batch-to-batch and beginning- to end-of-batch variability are shown to be adequately controlled.

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Question 15. Pseudoephedrine HCl Dissolution Profile

Aventis proposes using [

]

Does the Agency agree with this proposal?

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Division of Pulmonary and Allergy Drug Products

Question 15

Response

The concept is acceptable [

] for evaluation of batch performance over the shelf life of the drug product.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Question 16. Measurement of Impurities and Degradation Products in the Drug Product

Aventis proposes to [

]

Does the Agency agree with this proposal?

Response

Yes, this appears acceptable. We expect the acceptance criteria to accurately reflect your manufacturing capabilities if they improve on those exhibited in Allegra-D manufacture.

Question 17. [ ] Dissolution Test Method

To address FDA comments from EOP II meeting regarding the [ ] dissolution testing, Aventis proposes to provide dissolution data for pseudoephedrine HCl measured using the proposed test method [

]

Does the Agency accept this as addressing their request that pseudoephedrine dissolution data be generated [ ]

Question 17

Response

Dissolution data [ ] must be evaluated by both the CMC and Biopharm reviewers prior to agreement on a dissolution method and associated acceptance criteria. Since you have not provided data for evaluation, it is premature to comment on the appropriateness of the proposed parameters for the dissolution test method.

Provide dissolution data as requested in the EOP2 meeting.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Aventis responded that stability studies have been ongoing for [ ] months. Data will be provided in the NDA.

Additional Topic 18. [

]

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Additional Topic 18

Response

[redacted]

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Additional Topic 19. Fexofenadine HCl Drug Substance Particle Size.

Aventis has a batch history of [redacted] No changes to existing specifications are proposed, and, Aventis believes that additional evaluations of fexofenadine HCl dissolution performance [redacted] are unnecessary.

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Additional Topic 19

Response

This is acceptable for the [ ] provided that all manufacturing parameters are well defined and the stability data confirm reproducible stability results.

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Additional Topic 20. [ ]

[ ]

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Additional Topic 20

Response

Please comment on why [redacted]

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Additional Topic 21. Stability Database/Commitment.

As discussed during the End of Phase II meeting, Aventis will submit 12-months of ICH stability data for three batches in the NDA, and propose a 24-month expiration based upon the submitted database and the known stability of these drug substances. Statistical analyses will be performed on the assay and impurities data. Aventis will place the first three commercial production batches of this product on controlled room temperature (25°C/60% RH) stability and one batch annually thereafter. Aventis has made the recommended changes to the matrix stability protocol.

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Additional Topic 21

Response

Determination of the expiration dating period will be based upon statistical evaluation of all relevant parameters and must be calculated from real-time data. Differences in the stability data between similar containers may preclude poolability and hence adversely affect the calculated expiration dating period.

You must demonstrate that all physicochemical characteristics and functionality of the two proposed blister units are equivalent. If they show different characteristics or functionality and demonstrate different behavior on stability testing, then the container system that provides the least protection will be the limiting factor and be used to determine the expiration dating period.

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Aventis stated that they intend to provide the data from the stability analysis. The difference between the two proposed blister units is [ ]. One is the same as the blister unit used in the approved Allegra-D product.

Additional Topic 21

Response (Cont'd)

Considering the post-approval problems associated with Allegra-D 12 HOUR, and in order to confirm the proposed expiration dating period, the number of batches placed annually in the stability testing program must be [ ] of the production rate. Submit a proposal in the NDA [ ] This rate of batch stability testing will need to be implemented until the drug product stability and performance characteristics are verified.

The first three post-approval production-scale batches must be placed under accelerated storage conditions (40°C/75% RH) if the NDA stability batches are not production-scale batches.

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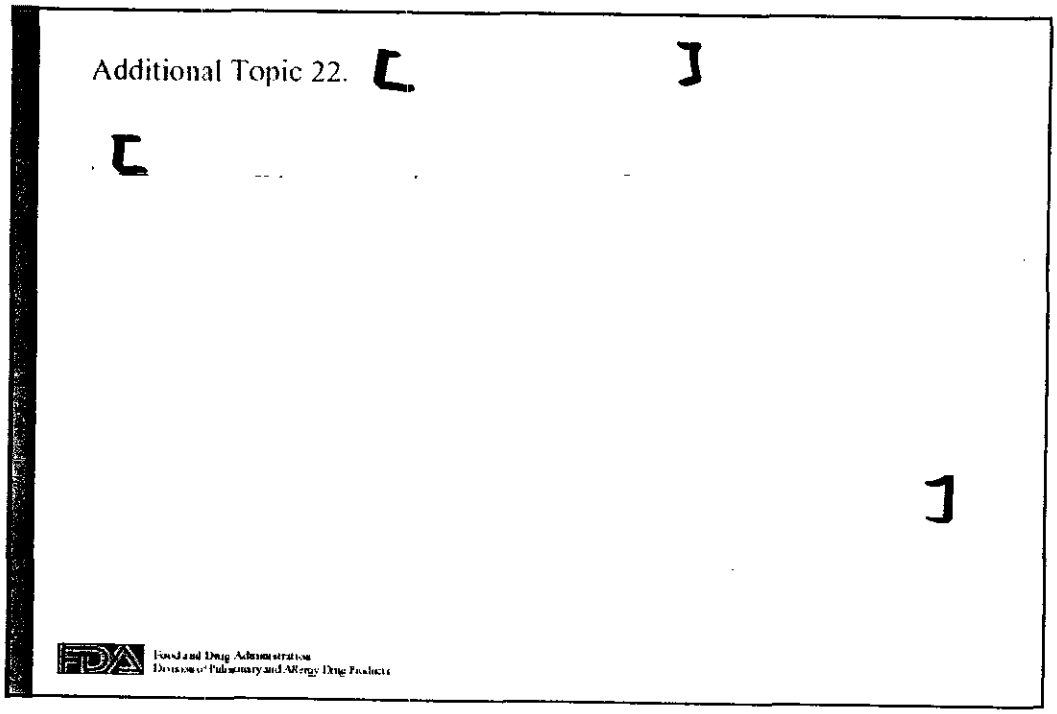
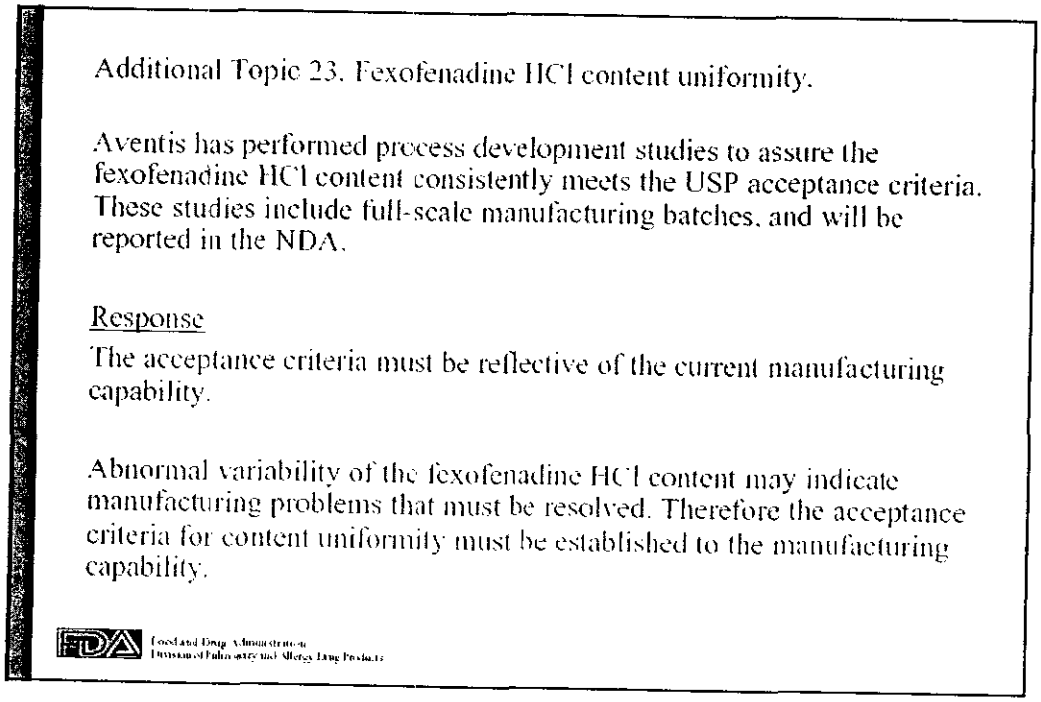


Upon inquiry from the Division, Aventis responded that [ ] is not an option.



Additional Topic 24. [ ]

[ ]

Response
Satisfactory. [ ]

Additional Topic 25. Label claim of pseudoephedrine HCl.

During the early development activities, some developmental batches were not manufactured at — label claim for pseudoephedrine HCl. The current manufacturing process accurately targets the pseudoephedrine HCl content at — of the label claim for the — tablets.

Response
Satisfactory

Additional Topic 26. Label claim of fexofenadine HCl.

Fexofenadine HCl [redacted] During early development batch manufacture, [redacted]

work identified the

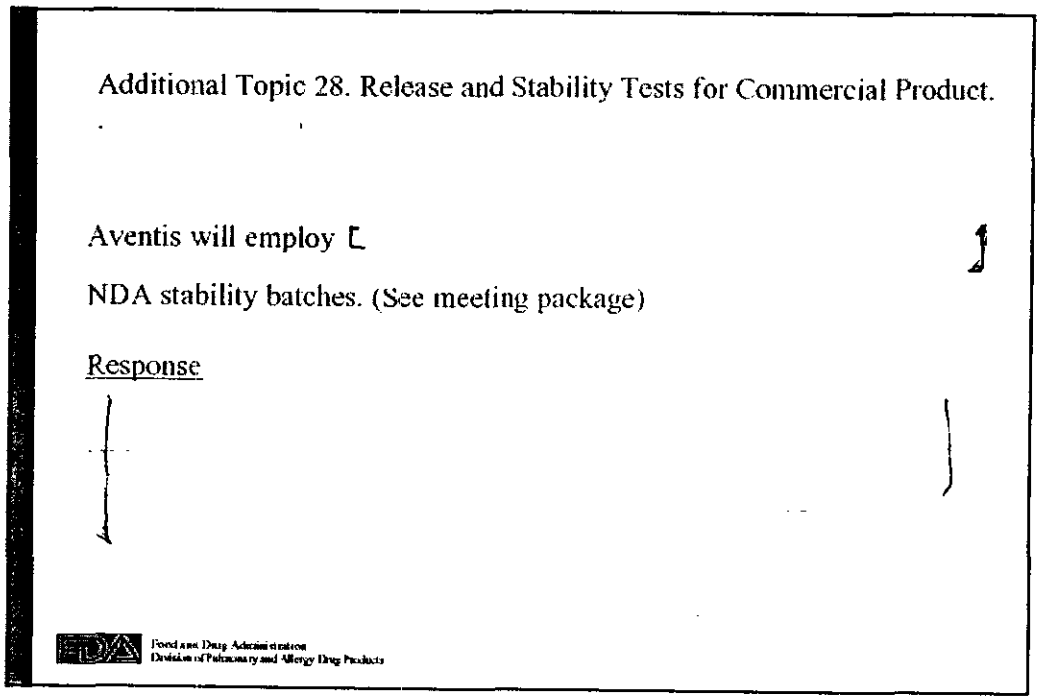
[redacted]

Response
Satisfactory

Additional Topic 27. DMF Letters of Access.

DMF Letters of Access for all noncompendial excipients will be provided in the NDA.

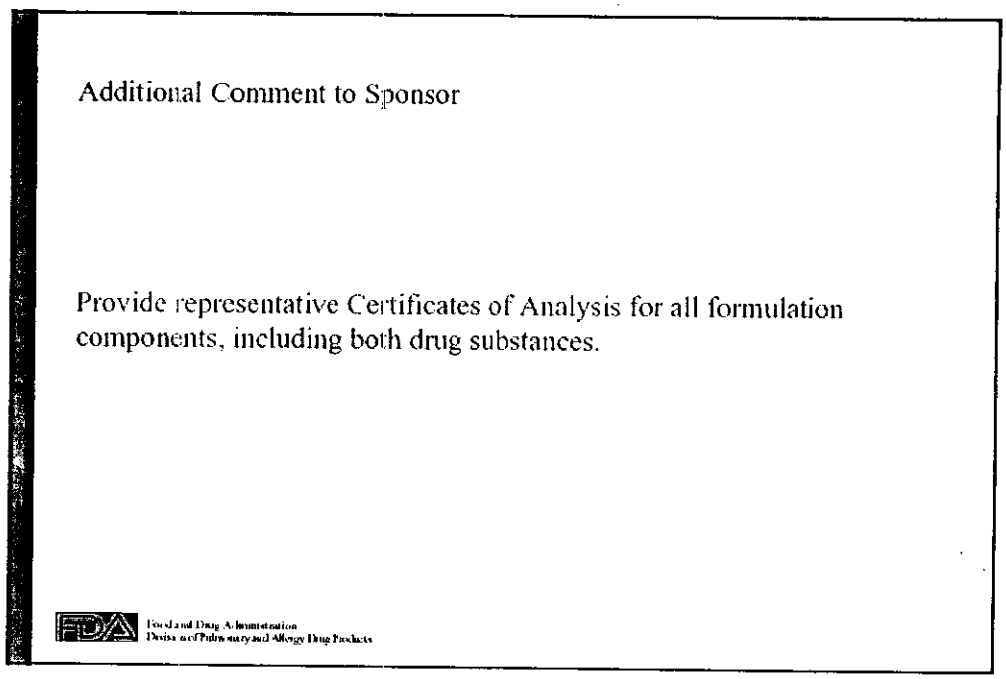
Response
Satisfactory



Aventis stated [

]

The Division recommended establishment of the — test method. Regarding a proposal [ ] Aventis should submit results of full-scale investigations as well as rationale for the proposed test. The Division referenced ICH Guidance on Q6A Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.



The meeting was adjourned at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Yu
9/25/03 06:05:43 PM

Memorandum of Telephone Facsimile Correspondence

Date: July 18, 2002

To: Eric Floyd, Ph.D.
Senior Director, Drug Regulatory Affairs

Fax: 908-231-3734

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: IND 48,486 Allegra-D 24-hour extended-release tablets
EOP2 January 29, 2002, Meeting Minutes

Reference is made to the meeting held between representatives of your company and this Division on January 29, 2002. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

INDUSTRY MEETING MINUTES

DATE:	January 29, 2002
LOCATION:	Parklawn Chesapeake Conference Room
Time:	1:30-3:00pm
APPLICATION:	IND 48,486
DRUG NAME:	Allegra-D (fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg) 24-hour extended-release tablets
SPONSOR:	Aventis Pharmaceuticals

BETWEEN:

Barbara Kittner, Clinical Manager
Susan Witham, Drug Regulatory Affairs
Eric Floyd, Drug Regulatory Affairs
[ ] CMC)
Damayanthi Devineni, Biopharmaceuticals
Sriram Krishnaswami, Biopharmaceuticals
Rajiv Haribhakti, Pharmaceutical Development
Kaz Chrzan, Pharmaceutical Development
Prafulla Agrawal, Pharmaceutical Development

AND

Division of Pulmonary & Allergy Drug Products, unless noted otherwise

Badrul Chowdhury, Medical Team Leader
Eric Duff, Director, Division of New Drug Chemistry II
Emmanuel Fadiran, Clinical Pharmacology & Biopharmaceutics TL
James Gebert, Biostatistics Team Leader
Shinja Kim, Clinical Pharmacology & Biopharmaceutics Reviewer
Charles Lee, Medical Reviewer
Marianne Mann, Acting Director
Mary Purucker, Medical Team Leader
Brian Rogers, Chemistry Reviewer
Jehan Rowlands, Post-doctoral fellow
Sandra Suarez, Clinical Pharmacology & Biopharmaceutics Reviewer
Christine Yu, Regulatory Project Manager
Feng Zhou, Mathematical Statistician

Background

Aventis Pharmaceutials requested an End-of-Phase II meeting to discuss with the Division their proposal for a 180 mg fexofendine and 240 mg pseudoephedrine extended-release tablet for once-a-day administration in treatment of seasonal allergic rhinitis in patients 12-years and older. The briefing package was received November 15, 2001.

Order of Agenda (based on questions submitted in briefing package)
Aventis presentation (3 slides)
A. Regulatory & related question #3 under Clinical Pharmacology
B. Chemistry, Manufacturing, and Control (CMC)
C. Clinical Pharmacology
D. Clinical
E. Labeling Question

Minutes Format
Aventis' questions from the briefing package are noted in Italics font, followed by the Division's responses and discussion in normal font.

Appendix A contains slides presented by Aventis during the meeting.
Appendix B contains slides presented by the Division during the meeting.
Appendix C contains CMC information presented during the meeting and faxed to Aventis on February 25, 2002.

Guidances for Industry referenced during the meeting
Note that guidances are not binding but rather represent the Agency's current thinking on the issue. Alternative approaches may be acceptable. Some guidances are in draft form for public comment. The content of draft guidances can change based on the review of public comments or other events.

Minutes
Aventis presented 3 slides highlighting details about the proposed drug product and the manufacturing process. The proposed drug product [ ]

A. Regulatory & Question #3 under Clinical Pharmacology

1. Question #3 under Clinical Pharmacology

Aventis plans to conduct these bioequivalence and food effect studies under the Allegra-D IND 48,486. Does the Division agree with this approach?

The Division does not agree. The new Allegra-D 24-hour formulation has an entirely different extended-release mechanism from the Allegra-D 12-hour formulation. The Division stated that since the two formulations are entirely different, a new IND should be submitted for the Allegra-D 24-hour formulation.

Aventis asked if the new IND may be waived of the 30-day safety waiting period.

The Division responded that with the submission of the new IND for the 24-hour formulation , Aventis can request a waiver of the 30-day safety waiting period.

2. Regulatory

Aventis plans to submit the new formulation and dosage regimen as an efficacy supplement under the Allegra-D NDA 20-786. Does the Division agree with this approach?

The Division does not agree. For the same reasons stated in Question 3 under Clinical Pharmacology, a new NDA should be submitted for the Allegra-D 24-hour formulation.

B. Chemistry, Manufacturing & Controls

1. *Aventis will be providing, in the efficacy supplement for the new formulation, stability data from three pilot scale-up batches. Aventis would like to submit the [ ] data from the three pilot scale-up batches with the initial filing of the supplement, then submit the [ ] and 12-month data at the 4-month safety update and prior to taking action on the NDA Supplement, respectively. Does the Division agree with this approach?*

Submit 12 months stability data with the application. Additional data may be submitted during the review process to support the proposed expiry.

2. *Allegra-D — stability data is expected to have a similar stability profile as observed for other formulations of fexofenadine HCl or pseudoephedrine HCl. Therefore, Aventis is proposing a 24-month expiry period with a commitment to place the first three marketed batches on stability. Does the Division agree with this approach?*

A 24-month expiry may be proposed. The labeled expiry will be based on the quality and extent of stability data received.

3. *Please confirm that our proposed product specifications are acceptable, recognizing that dissolution specifications will be redefined based on NDA registration batch data.*

- Product specifications will be based upon the data from all critical batches, including the available stability data. Since neither appropriate methods nor data for dissolution are provided, comments are withheld at this time.

- The specification should contain a second identity test that is not based on [ ] (HPLC — acceptable, — not acceptable).

- We expect that the related impurities specifications will be as tight or tighter than those for Allegra-D 12-Hour Tablets. Also, the acceptance criteria for process-related impurities must be listed and included in the limits for Total Related Impurities. A footnote may be added to clarify that the process-related impurities are analyzed at the drug substance level. A parameter for Individual Unspecified Impurities must be

included with limits of Less Than [ ] Also, the parameter Total Unspecified Impurities must be included and limits set.

- The limits for related impurities must be provided for two significant figures. [

  ]

- The levels [ ] should be minimized.

- Among other variables, [

  ] should be evaluated. The registration stability batches must be manufactured and placed on stability only after you establish the optimized parameters for this drug product.

- A specification for Karl Fisher moisture content must be included. Acceptance criterion must be based upon the levels validated in the previously mentioned study.

- Owing to the possibly inaccurate nature of the fexofenadine HCl [appropriate validation studies must be accomplished to demonstrate the suitability of the — for the fexofenadine HCl [ ]These validation studies must include scale-up and process variable effects.

- We expect 100% inspection for [ ]

- We note that the assay values for pseudoephedrine HCl are [ ] and the assay values for fexofenadine HCl are [ ] in the data for the developmental batches on page 32, 40, 58, 60, 72, 74, etc. Manufacture of the pseudoephedrine [ ] the fexofenadine [ ] of Label Claim.

- Letter of authorization (LOA) for Drug Master Files (DMFs) will be needed for all non-compendial excipients.

4. *Aventis has proposed a matrix program for the Allegra-D — batches which will be placed on stability for the new formulation. The proposed stability matrix program is based on the currently known stability information for the new Allegra-D — formulation development batches and stability data of marketed Allegra products. The enclosed matrix stability protocol is based on the draft stability guidance document and we believe it meets the criteria for matrixing design package product evaluations. Please confirm that the stability protocol, including the testing to be performed, is acceptable.*

The protocol needs to be modified to provide for testing of all presentations at 12 and 24 months since 12 months data is required at submission and a 24-month expiry is being proposed.

5. *Note that the dissolution method we have been using for this new formulation has* [redacted]

Aventis proposes to collect data using [redacted] *Does the Division have any comments on this plan?*

- Product specifications will be based upon the data from all critical batches, including the available stability data. Since neither appropriate methods nor data for dissolution are provided, comments are withheld.
- [redacted]
- We also refer to the previous comment 3 [redacted]
- Recommendations for media and dissolution conditions will be addressed by the Clinical Pharmacology & Biopharmaceutics reviewer.

C. Clinical Pharmacology & Biopharmaceutics

1. Response to question #5 under CMC

In selecting the dissolution method, consider the effect of medium (pH), apparatus and speed on the dissolution of both components of the formulation. Also provide the optimized dissolution method with specifications for fexofenadine and pseudoephedrine.

2. *Aventis will be conducting a bioequivalence study and a food effect study to support the approval of the new formulation for Allegra-D (180 mg fexofenadine HCl and 240 mg pseudoephedrine HCl) extended-release tablets taken once a day. Does the Division agree with this approach?*

Conduct a multiple dose study (to characterize the steady state performance of the product).

3. *Does the Division have any comments on the study designs proposed for the bioequivalence and food effect studies?*

   a. Please include females in the proposed studies. Consider the following statements in the FDA guidances:

      - "If the drug product is intended for use in both sexes, the sponsor should attempt to includes similar proportions of males and females in the study" (Guidance for Industry, "Bioavailability and Bioequivalence studies for orally administered drug products- General considerations").

      - "Gender should not be an inclusion criteria" (Guidance for Industry, "Study and evaluation of gender differences in the clinical evaluation of drugs").

   b. Please set the confidence interval for food effect on C max to 80 to 125% or provide justification (PK/PD relationship) for using a different criterion.

   c. The to-be marketed formulation should be used for these studies. If not, then Aventis should link the formulation used in these studies (i.e., BE/food effect) to the to-be marketed formulation.

D. Clinical

1. Protocol comments

   - It is not acceptable to exclude females from the pivotal bioequivalence and food effect studies. Gender should not be an inclusion criterion. Females should be represented in the BE studies, and not uniformly excluded as per the current protocols.

   - We strongly recommend that you use the final, to-be-marketed formulation in the pivotal studies

   - Provide data for C_{min} in addition to AUC and C_{max}. We will look at data for C_{min} to support end-of-dosing-interval bioavailability.

   - Safety endpoints are acceptable.

2. Additional comments

   - There is evidence that grapefruit and apple juices affect fexofenadine bioavailability. It is recommended that you study the effects of apple and grapefruit juices on fexofenadine bioavailability.

- It appears that the proposed trade name for your product is "Allegra —" The trade name is not likely to be acceptable. An alternative trade name would be "Allegra-D 24 Hour," which more accurately reflects the proposed dosing interval.

- Upon approval, the trade name of the current Allegra-D (12-hour dosing) product must be changed accordingly to decrease confusion with the new product. An alternative trade name for the current product would be "Allegra-D 12 Hour."

3. Clinical question from briefing package

Aventis will be requesting an official waiver of pediatric studies as currently required by the Pediatric Rule based on the amount of pseudoephedrine contained in the new formulation, and that it is unsafe for children under the age of 12 years. Does the Division agree that pediatric studies in children under the age of 12 years will not be required in order to get approval for the new Allegra-D formulation?

Pediatric studies will not be required for approval of the Allegra-D 24-hour formulation.

E. Labeling Question

Three studies evaluating special populations in renally-impaired, hepatically-impaired patients and elderly patients were previously submitted and reviewed under NDAs 20-872 and 20-786. These studies support the current approved labeling for Allegra-D and Allegra tablets. Aventis is planning to submit draft labeling for the new Allegra-D formulation which will provide the same text that is currently in the Allegra labeling under Special Populations. Does the Division agree with this proposal?

- The Special Populations section of the current Allegra-D label will not be acceptable for the new formulation. The current labeling contains a recommended starting dose for renally-impaired patients. This is likely to be an inappropriate starting dose of the new Allegra-D formulation for renally-impaired patients.

- You must be prepared to support your recommendations, including recommended dose, if you propose use of this product in this population.

The meeting concluded at this time.

13 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Yu, Christine

'om: Jones, Michael D
:nt: Friday, January 25, 2002 4:21 PM
To: Mann, Marianne C
Cc: Yu, Christine; Jones, Michael D; Brice, Tawni M; Friedman, Beverly J
Subject: RE: follow-up on our dosage form question: Allegra D-24 hour tablets

Marianne

It sure seemed like the two drug products were quite different. However, they appeared to both be extended release tablets (with the same ACTIVE ingredients). The only way that I thought that you could "make" them come in as a separate NDA was the excepient clause. I gather from what you tell me that won't do the trick either.

That just leaves us the administrative convenience route. If they want to submit a supplement they could. But we could ask for an NDA for our own administrative convenience but would assess the new NDA as if it were a supplement.

It looks like from what you tell me the "precedent" case was administered correctly, however, it does not seem to directly correspond to our current problem so I don't see any "precedent" problems.

So ... if the new novel extended release tablet is not a new dosage form (Orange Book terms) nor is it a new route of administration (Orange Book terms) nor can we use the excepient argument, it looks like a supplement fee. It should be documented (a memo to the file would be appropriate) when the application comes in why we are charge a 1/2 fee rather than a full NDA fee.

If you wish you can speak to the applicant and tell them our determination giving the caveat that if things change once we receive the application (e.g., it really wasn't a tablet, but a capsule) our determination may change.

I hope this is helpful.

't me know how it goes.

Mike

-----Original Message-----
From: Mann, Marianne C
Sent: Friday, January 25, 2002 3:58 PM
To: Jones, Michael D
Cc: Yu, Christine
Subject: follow-up on our dosage form question: Allegra D-24 hour tablets

Hi Mike,
Chris Yu already posed the question to you about whether Aventis pharmaceuticals could submit their data for Allegra-D-24 hour tablets under their current NDA for Allegra-D-12 hour tablets.

You had replied that there is a clause, under exipients, in the bundling policy that states:

"Differences in excipients that require separate clinical studies of safety or effectiveness should not be included in the same original application."

In this situation, the new Allegra-D-24 hour formulation is QUITE different, but there are no exipients that require additional separate clinical studies. Nonetheless, our chemists assure me that the Allegra-D-24 hour drug product is entirely novel, and quite different from, the Allegra-D-12 hour drug product. Their application will consist of appropriate chemistry information, a single crossover bioequivalence study, and a single-crossover food effect study. It's fairly straight-forward in this regard.

At our meeting with the sponsor, I was going to therefore tell them that we would ask for a separate NDA for the Allegra-D-24 hour drug product. As for user fees, I would leave it to your consideration as to whether or not they should pay a FULL fee, or a supplemental fee.

The only clear precedence we have for this is Claritin-D-12 and Claritin-D-24 hour tablets-----which were approved under separate NDAs. I believe they each paid full user fees, and that the sponsor did not "bundle" because the initial

submission was not approved.....and therefore they couldn't "bundle."

Please let me know if you agree with my position! Thanks for your input on this! If you have any input on the user fee, I could share this with them, but if you'd prefer to wait till the application arrives.....I will not commit!~

-Marianne (deputy in DPADP)

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On Original